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REVIEW ARTICLE

Understanding exosomes: Part 2—Emerging leaders in regenerative medicine

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Abstract

Exosomes are the smallest subset of extracellular signaling vesicles secreted by most cells with the ability to communicate with other tissues and cell types over long distances. Their use in regenerative medicine has gained tremendous momentum recently due to their ability to be utilized as therapeutic options for a wide array of diseases/conditions. Over 5000 publications are currently being published yearly on this topic, and this number is only expected to dramatically increase as novel therapeutic strategies continue to be developed. Today exosomes have been applied in numerous contexts including neurodegenerative disorders (Alzheimer's disease, central nervous system, depression, multiple sclerosis, Parkinson's disease, post-traumatic stress disorders, traumatic brain injury, peripheral nerve injury), damaged organs (heart, kidney, liver, stroke, myocardial infarctions, myocardial infarctions, ovaries), degenerative processes (atherosclerosis, diabetes, hematology disorders, musculoskeletal degeneration, osteoradionecrosis, respiratory disease), infectious diseases (COVID-19, hepatitis), regenerative procedures (antiaging, bone regeneration, cartilage/joint regeneration, osteoarthritis, cutaneous wounds, dental regeneration, dermatology/skin regeneration, erectile dysfunction, hair regrowth, intervertebral disc repair, spinal cord injury, vascular regeneration), and cancer therapy (breast, colorectal, gastric cancer and osteosarcomas), immune function (allergy, autoimmune disorders, immune regulation, inflammatory diseases, lupus, rheumatoid arthritis). This scoping review is a first of its kind aimed at summarizing the extensive regenerative potential of exosomes over a broad range of diseases and disorders.

KEYWORDS
dermasomes, exosomes, immunosomes, regenerative medicine, ultra-centrifugation

1 | INTRODUCTION

Exosomes are the smallest extracellular vesicles ranging in size from 30 to 150 nm and are found in the majority of bodily fluids.[1] They can transport functional miRNAs, coupled with the inherent biological functions of exosomes, which makes them a highly sought after and novel delivery platform.[2] Specifically, they have the characteristics of low immunogenicity and high transport efficiency, which can regulate inflammation and cross the blood–brain barrier (BBB).[3–5] They transport signaling molecules that drive a number of biological

processes, including cell signaling, immunological responses, tumor metastasis, and other biological activities. Exosomes have now been shown in several investigations to play both diagnostic and therapeutic functions, in which their precise detection, separation, and quantification are crucial. Today, exosomes are one of the most highly researched topics in regenerative medicine with over 5000 publications being published on the topic yearly. Part 1 of this three-part series on exosomes focused on exosome biogenesis as well as their standard isolation techniques, including ultra-centrifugation, microfluidic, immunoaffinity, precipitation, size-exclusion chromatography, ultrafiltration technologies. This second article is focused on the therapeutic potential of exosomes in medicine. It is divided into eight categories highlighting the therapeutic potential of exosomes as follows:

- Neurodegenerative disorders: Alzheimer's disease, central nervous system, depression, multiple sclerosis, Parkinson's disease, post-traumatic stress disorders, traumatic brain injury, peripheral nerve injury.
- Treatment of damaged organs: heart, kidney, liver, stroke, myocardial infarctions, myocardial infarctions, ovaries.
- Degenerative processes: atherosclerosis, diabetes, hematology disorders, musculoskeletal degeneration, osteoradionecrosis, respiratory disease.
- Treatment of infectious diseases: COVID-19, hepatitis.
- Regenerative procedures: antiaging, bone regeneration, cartilage/joint regeneration, osteoarthritis, cutaneous wounds, dental regeneration, dermatology/skin regeneration, erectile dysfunction, hair regrowth, intervertebral disc repair, spinal cord injury, vascular regeneration.
- Cancer therapy: breast cancer, colorectal cancer, gastric cancer, and osteosarcomas.
- Improvements in immune function: allergy, autoimmune disorders, immune regulation, inflammatory diseases, lupus, rheumatoid arthritis.
- Treatment of random disorders: infertility, obesity, and sleep apnea.

The aim of this scoping review is to summarize the extensive regenerative potential of exosomes over a broad range of disorders and to elaborate on the potential clinical relevance of this novel treatment approach.

2 | EXOSOMES AND NEURODEGENERATIVE DISEASE

The medical community is persistently seeking appropriate treatment solutions for neurodegenerative illnesses due to the limitations of short-term symptomatic therapy and the dose-dependent adverse effects associated with pharmaceutical treatments. This pursuit is driven by the recognition of neurodegenerative disorders as a significant global health problem.[6] The identification regarding the therapeutic potential of stem cells for the treatment of neurodegenerative illnesses dates back to 1980 when Parkinson's disease (PD) was treated using fetal nerve tissue. Subsequently, a multitude of comprehensive investigations have been undertaken to formulate an effective therapeutic approach for the treatment of neurological disorders. Currently, there is a significant body of knowledge on the therapeutic potential of stem cells and their secreted factors in the context of treating neurodegenerative illnesses. This novel framework has shown distinct attributes pertaining to this therapeutic approach, including neuroprotective and neurodegenerative effects, remyelination capabilities, mitigation of brain inflammation, and restoration of functionality subsequent to produced damage.[6] Nevertheless, the precise method by which stem cells facilitate the healing of nerve injury remains uncertain. One significant component of their secretory function, exosomes, has been proposed as a key contributor to these therapeutic benefits. A multitude of research conducted in recent decades has examined the therapeutic efficacy of exosomes in the management of many neurological disorders. The primary objective of this review article is to examine the potential of stem cell-derived exosome-based treatments in the context of treating and managing neurodegenerative disorders.[6]

Regrettably, the occurrence of diverse neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), PD, multiple sclerosis (MS), Alzheimer's disease (AD), and Huntington's disease (HD), has been attributed to the progressive deterioration of neuronal function and structure in both the peripheral and central nervous systems.[7] The process of aging is well recognized as the primary risk factor for several brain disorders.[8] With the global elderly population seeing significant growth, it is anticipated that degenerative neurological illnesses will surpass cancer in the foreseeable future, therefore becoming the second most prevalent cause of mortality worldwide.[9] Neurodegenerative disorders have a significant influence on several aspects of individual functioning, including but not limited to balance, motor skills, cognitive abilities, language proficiency, and respiratory function.[10] While the etiology of several illnesses remains unclear, a confluence of hereditary and environmental variables might potentially contribute to their development.[10] Most often, these disorders cause neurons to die thus affecting distinct parts of the brain, such as the striatal regions in PD and the cortical and hippocampal regions in AD.[11] These conditions may present with minor or severe symptoms, depending on the part of the brain that is impacted.[12] The presence of these diseases, characterized by their prolonged duration and significant treatment expenses, poses a substantial challenge for both patients and the healthcare community. Consequently, considerable efforts are being directed toward the development of efficacious treatments to address this global issue.

Currently, there is a lack of definitive cures for these diseases, with the majority of treatment approaches in Western Medicine focusing on symptom management, pain relief, symptom control, and enhancement of mobility.[11] During the 1970s, the first pharmacotherapy groups centered on target-based approaches emerged, serving as substitutes for second messenger modulators, direct

receptor agonists, enzyme inhibitors, releasing agents, and neurotransmitters. Among the first generation of these drugs are those used to replace dopamine, such as dopaminergic drugs,[13] acetylcholinesterase inhibitors,[14] analgesic drugs,[15] and surgical treatments, like deep brain stimulation, for the management of many movement disorders.[16] Cholinesterase inhibitors, another significant family of FDA-approved medications used to treat all stages of AD since 1978, and L-DOPA (L-3,4-dihydroxyphenylalanine), the first drug authorized for the clinical treatment of PD.[17–20] The goal of the second generation of these medications is to halt and reduce the disease's development. Examples include riluzole for Huntington's disease, cerebellar ataxia, and ALS[21]; nonsteroidal anti-inflammatory medications (NSAIDs) that lower the risk of AD with long-term usage[22]; and CERE-120 (adeno-associated virus serotype 2-neurturin), which is in phase I study for people with idiopathic PD.[23–25]

The blood–brain barrier (BBB) is a specialized membrane that exhibits extreme selectivity in its permeability, effectively restricting the passage of big molecules and almost all small molecules from peripheral organs to the brain. Due to this rationale, a range of intrusive methodologies have been devised or are currently being explored to overcome the selective nature of the BBB. These procedures include neurosurgery, the biochemical manipulation of the BBB, and the use of diverse nanoparticle formulations. Nevertheless, these strategies are not without their limitations in the context of drug administration since they may encounter challenges related to the fast elimination of drugs by the mononuclear phagocyte system. Multiple studies have provided evidence suggesting that exosomes possess the ability to traverse the BBB and surmount the immune-privileged nature of the brain, resulting in a decrease in medication elimination. Significantly, exosomes possess the capability to cross the BBB and convey proteins and RNAs into the brain via various routes of administration, such as intranasal, intravenous, intraperitoneal, and intracranial methods. This observation underscores the considerable adaptability and suitability of exosome-mediated drug delivery for the treatment of central nervous system (CNS) disorders.

Therefore, exosomes have been used as a therapeutic intervention for many chronic degenerative neurological disorders. The conditions encompassed in this list are Alzheimer's disease, central nervous system diseases, depression, multiple sclerosis, neurodegenerative disease, Parkinson's disease, post-traumatic stress disorders, and traumatic brain injury. Numerous studies have indicated the clinical efficacy of these treatments, as will be discussed in the following sections.

2.1 | Alzheimer's disease

Alzheimer's disease is a common neurological illness that affects a significant number of people worldwide. Unfortunately, there are few therapeutic options available that have been proven efficacious. The primary strategy for therapeutic intervention in Alzheimer's disease involves the use of inhibitors targeting the enzyme BACE-1 in both neurons and glial cells. This technique effectively reduces the levels of A-beta, the principal peptide associated with Alzheimer's pathology. The efficacy of drugs utilized for AD is often limiting since they must be taken following early diagnosis. The maintenance of homeostasis and normal brain function relies on cellular interactions within the brain. Exosomes have been identified as significant contributors to cell-to-cell communication among brain cells, facilitating the transfer of information from one cell type to another. It is noteworthy that extracellular vesicles released by mesenchymal stem cells have shown superior efficacy compared with the corresponding parent cells.[26] Exosomes possess several advantages upon their specific fusion with target cells. Firstly, they effectively exclude the heterogeneity present in the original cells through a precise selection process. Additionally, their engineering and drug accumulation capabilities enable them to exhibit molecular specificity. Exosomes are capable of inducing effective actions by leveraging variable concentrations of molecules and factors, as well as activating signaling cascades. The strength of their position is enhanced by their integration with a multitude of elements and activities.[26]

Exosomes have been seen to exert their effects on neuronal and glial cells, facilitating the healing process after traumas and immunological responses.[26] The fusion of MSC-Exos has been found to be crucial in facilitating intercellular communication among brain cells, both in healthy conditions and in the context of different pathological states. Several protective effects have been documented, such as the facilitation of synaptic plasticity, provision of nutritional and metabolic assistance, promotion of neuron regeneration, modulation of inflammatory response, and removal of toxic elements.[27,28] Both the brain and spinal cord may be subject to the induction of traumas and ischemia lesions. In several instances, it has been shown that the recuperation facilitated by modest dosages of MSC-Exos starts via the stimulation of a limited number of receptors. Subsequently, this leads to the phosphorylation of kinases (and other factors), as well as the activation of miRNAs.[28–31] Similarly, it has been shown that MSC-Exos had the ability to alleviate trained immune responses initiated by innate cells, resulting in specific localized tissue healing.[32] Furthermore, MSC-Exos have been shown to regulate neuronal responses and mitigate the detrimental effects caused by glial cells, including astrocytes and microglia.[33,34]

Preclinical research on MSC-Exos has been extensively conducted in murine models, with favorable results (Figure 1). The primary processes behind these effects include the release of secreted mesenchymal stem cell-derived extracellular vesicles (MSC-Evs) including their cargo, which contains crucial components such as nucleic acids, as well as other therapeutic agents. One of the significant impacts associated with AD is the downregulation of BACE-1 and Aβ levels, accompanied by an elevation in sphingosine-1-phosphate. These events are generated by the protective action of extracellular vesicles derived from MSC-Exos against neuronal damage caused by AD.[35–37] As a result, the simple injection into the tail vein of animal models has been shown to produce positive effects on the mouse brain including ameliorating cognitive impairment and reducing A-beta aggregation as well as neuronal death.[38] Action potentials, dendritic spine augmentations, [Ca^{2+}] oscillations, and mitochondrial

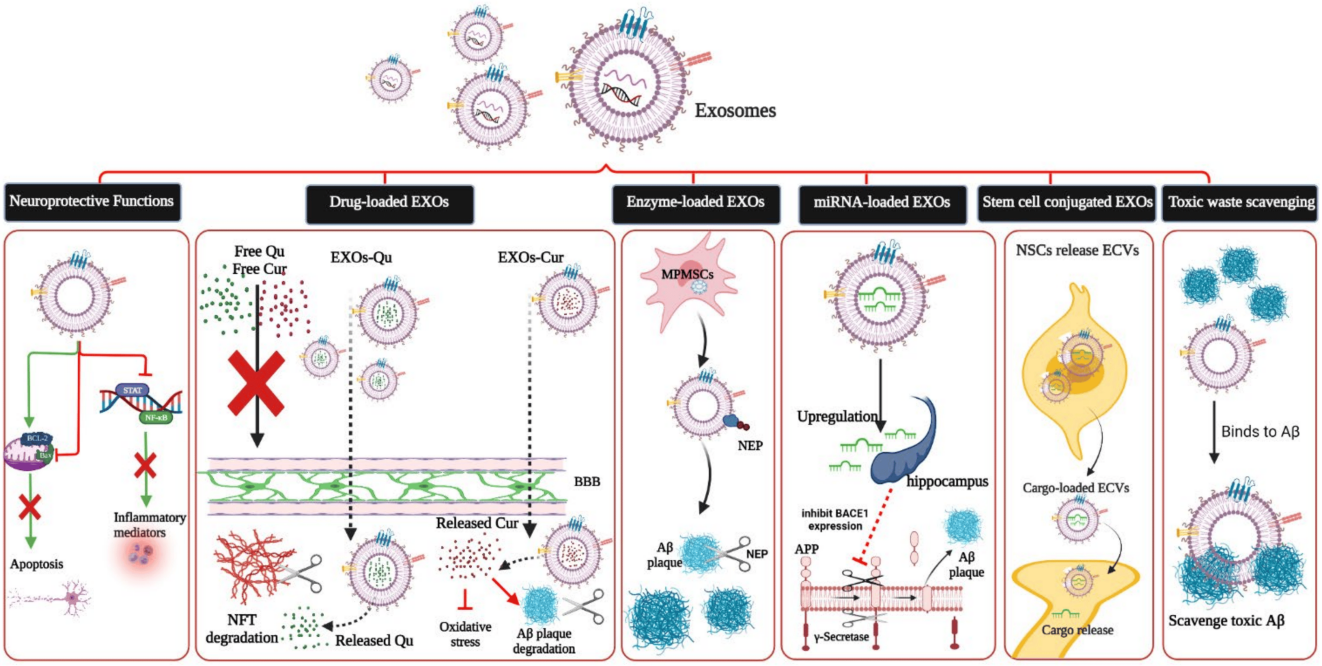

FIGURE 1 Therapeutic application of exosomes in AD. A, amyloid-beta; APP, amyloid precursor protein; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; BaX, BcL-2-associated X protein; BBB, blood–brain barrier; BCL2, B-cell lymphoma 2; Cur, curcumin; ECVs, extracellular vesicles; MP-MSCs, multipotent mesenchymal stem cells; NEP, neprilysin; NF-B, nuclear factor kappa-light-chain enhancer of activated B cells; NFT, neurofibrillary tangles; NSCs, neural stem cells; QU, quercetin; STAT, signal transduction and activator of transcription protein. 1081×540 mm (118×118 DPI). Reprinted with permission from Soliman et al.[40]

reactivations are among the effects that MSC-Exos restore.[38] Recent findings have shown MSC-Exos demonstrate great promise as a therapeutic agent and biomarker for AD in humans.[39–41] The symptoms that were reported, such as the return of homeostatic levels, the preservation of synapses, and enhanced cognition, are comparable to those shown in mice.[42] In actuality, MSC-Exos prevent neurodegeneration in AD and many other disorders, having favorable effects on brain regeneration and tissue repair.[43] A growing body of research indicates that exosomes facilitate cell–cell communication in the brain, which enables them to reduce neuroinflammation and enhance the control of synaptic function. The utilization of exosomes in AD as a therapeutic target or as a biomarker for early identification has been covered in a number of review articles over the years.[26,40,44–49]

2.2 | Parkinson's disease

The use of exosomes as a therapeutic intervention for Parkinson's disease has garnered significant attention due to the escalating global prevalence of the condition. PD is a progressive movement condition and the second most prevalent neurological illness behind Alzheimer's that impacts around 2% of those aged over 65 years.[50] Resting tremors, stiffness, slowness, and inability to maintain balance are all examples of motor symptoms. As dopaminergic neurons of the substantia nigra pars compacta die off over time, surviving neurons develop abnormal structures called Lewy bodies (LBs) and Lewy neurites (LNs) due to the accumulation of the synaptic protein alpha-synuclein (-syn).[51] The neurotransmitter dopamine (DA) is depleted as a result of these alterations, and an imbalance between acetylcholine (ACH) and DA occurs, resulting in motor difficulties.[50,52]

RNA molecules, antioxidants, and dopamine agonists are some of the treatments now available to help reduce the motor symptoms associated with Parkinson's disease. Medication for PD nonmotor symptoms include secondary side effects such as sadness, exhaustion, sleeplessness, and dementia.[53–55] Nevertheless, the efficacy of these medications in halting the ongoing dopaminergic damage is limited due to the reduced efficiency of drug transport caused by the BBB. Similar to several other neurological illnesses, the insufficient permeability of the BBB has been a challenge in the administration of therapeutic interventions for PD in the brain.

In recent years, exosomes have gained significant attention in the field of neuroscience, particularly in the context of neurological disorders such as stroke and brain tumors owing to their ability to cross the BBB. This heightened interest may be attributed to the remarkable biocompatibility shown by exosomes, their capacity to cross the BBB without inducing toxicity, and their ability to selectively target specific sites within the brain. The capacity of exosomes to readily cross the BBB without thrombotic concerns and integrating into neurons and glial cells has also provided the potential for utilizing nano-sized Exos as vehicles for therapeutic medicines or bioactive proteins.

Jarmalaviciute et al.[56] were one of the first to investigate the neuroprotective capabilities of extracellular vesicles (EVs) in an in vitro model using dopaminergic neurons subjected to 6-hydroxy-dopamine (6-OHDA) induced toxicity. Human exfoliated deciduous teeth were used to grow cultures of mesenchymal stem cells from the dental pulp. Dopaminergic neurons generated from neural stem cells were shielded against 6-OHDA when EVs were present in the growth medium. Thus, exosomes isolated from the tooth pulp prevented 6-OHDA-induced death of 80% of dopamine neurons.[56]

Using a 6-OHDA model of PD in rats, in which 6-OHDA was injected into the medial forebrain bundle (MFB), a subsequent investigation showed that MSC-EVs delivered intranasally enhanced treatment success.[57] Eight days after unilaterally injecting 6-OHDA into MFB, animals who received daily Exo therapy for 15 days had substantial improvements in gait metrics and motor function. The results demonstrated that Exos from MSCs alleviated Parkinsonian symptoms in a rat model.[57]

Similar outcomes were also seen in a different study when conditioned medium from human dental pulp stem cell cultures were administered in the PD animal model.[58] In a 6-OHDA rat model of Parkinson's disease, the impact of intravenous hUC-MSC-EV treatment (200 μg, every third day for 8 weeks) was investigated. Exos were shown to penetrate the BBB and integrate into the substantia nigra where they decreased apoptosis, thereby safeguarding dopaminergic neurons and elevating dopamine levels in the striatum. The Exo-treated animals also displayed diminished asymmetric rotation in response to apomorphine treatment at 8 weeks after transplantation.[59]

Haney et al.[60] created EVs by transfecting macrophages demonstrating promise for the treatment of PD. By introducing a plasmid DNA (pDNA) containing the catalase gene into macrophages using electroporation, the resulting transfected macrophages released EVs that contained various components such as catalase genetic material (pDNA and mRNA), functional catalase, and NF-kB. These EVs were effectively transferred to neurons, leading to a notable decrease in inflammation and the activation of neuroprotective mechanisms in the animal model utilized for PD.[60]

A notable study by Zhuang et al.[5] observed that exosomes obtained from MSCs loaded with curcumin, a low molecular weight compound with anti-inflammatory properties exhibited a reduction in the activation of microglial cells involved in inflammation. Consequently, these exosomes provided protection against brain inflammation induced by lipopolysaccharides (LPS) in mice.[5] Additionally, even MSC-Exos injected intraperitoneally were quickly absorbed by cells in the mice's brain, including microglial cells that were both active and in a resting state.[5]

In light of this, these combined results provides encouraging preclinical results regarding the use of exosomes as effective PD treatment alternatives with many review articles written on the topic[61–65] with Figures 2 and 3 summarizing these findings.

2.3 | Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease of the CNS that causes the brain and spinal cord to develop numerous demyelinating lesions. It affects the lives of an estimated 2.8 million individuals globally.[66] A diverse range of symptoms, including exhaustion, impairment of bladder and bowel function, visual deficits, difficulties with mobility and coordination, as well as sensory abnormalities. Individuals diagnosed with MS have significant cognitive and emotional alterations that have a profound impact on their overall quality of life. The occurrence of myelin loss or demyelination may result in neuronal disruption, perhaps accompanied by alterations in axonal structure, hence giving rise to a variety of neurological symptoms. In the relapsing–remitting type of MS, these symptoms may transiently manifest for extended periods of time (weeks) during disease exacerbation (known as relapse). Despite the identification of many genetic, metabolic, and environmental variables that influence the development of MS, there is a lack of comprehensive understanding of the specific processes involved in the damage to CNS tissue. Recent research has shown the substantial involvement of circulating extracellular vesicles in several pathological conditions. Exosomes have been identified as a crucial means of intercellular communication, facilitating the exchange of information between two distinct cell types, whether they are located in close proximity or in different regions of the body. In light of recent advancements in comprehending the pathophysiology of MS, investigations have unveiled diverse EVs and their respective functions in the progression of MS. These EVs hold potential as biomarkers for the purpose of monitoring the advancement of the condition. Moreover, their complete understanding will allow exosomes to be used as therapeutic options with the goal of potentially reversing the disease.

The immune-mediated damage occurring in the CNS of individuals with MS is a result of intricate interactions involving several types of immune cells, including NK cells, macrophages, dendritic cells, B cells, and T cells.[67–69] Glial cells, including astrocytes and microglia, function as nonclassical immune cells in the pathophysiology of multiple sclerosis in addition to other immune cells.[70–73] Exosomes are thought to be very effective therapeutic options for the treatment of human illnesses, such as MS. Recent research has shown that in animal models of progressive multiple sclerosis, MSC-Exos may aid in the recovery from demyelination.[74–77] Notably, MSCs transfer has been studied as a cell treatment for multiple sclerosis for many years, with varying degrees of success. Studies have found that MSC-Exos increased microglial polarization and decreased cytokine production including IL-6, IL-12p70, IL-17AF, and IL-22.[74–77]

Recently, Casella et al. created a murine microglial cell line that generates EVs loaded with IL-4 that exhibit the endogenous "eat me" signal Lactadherin (Mfg-e8) on their surface. After only one injection of the modified EV, the mice with induced encephalitis showed less neuroinflammation and a lower EAE clinical score, which was linked to an increase in anti-inflammatory markers in phagocytic cells.[78]

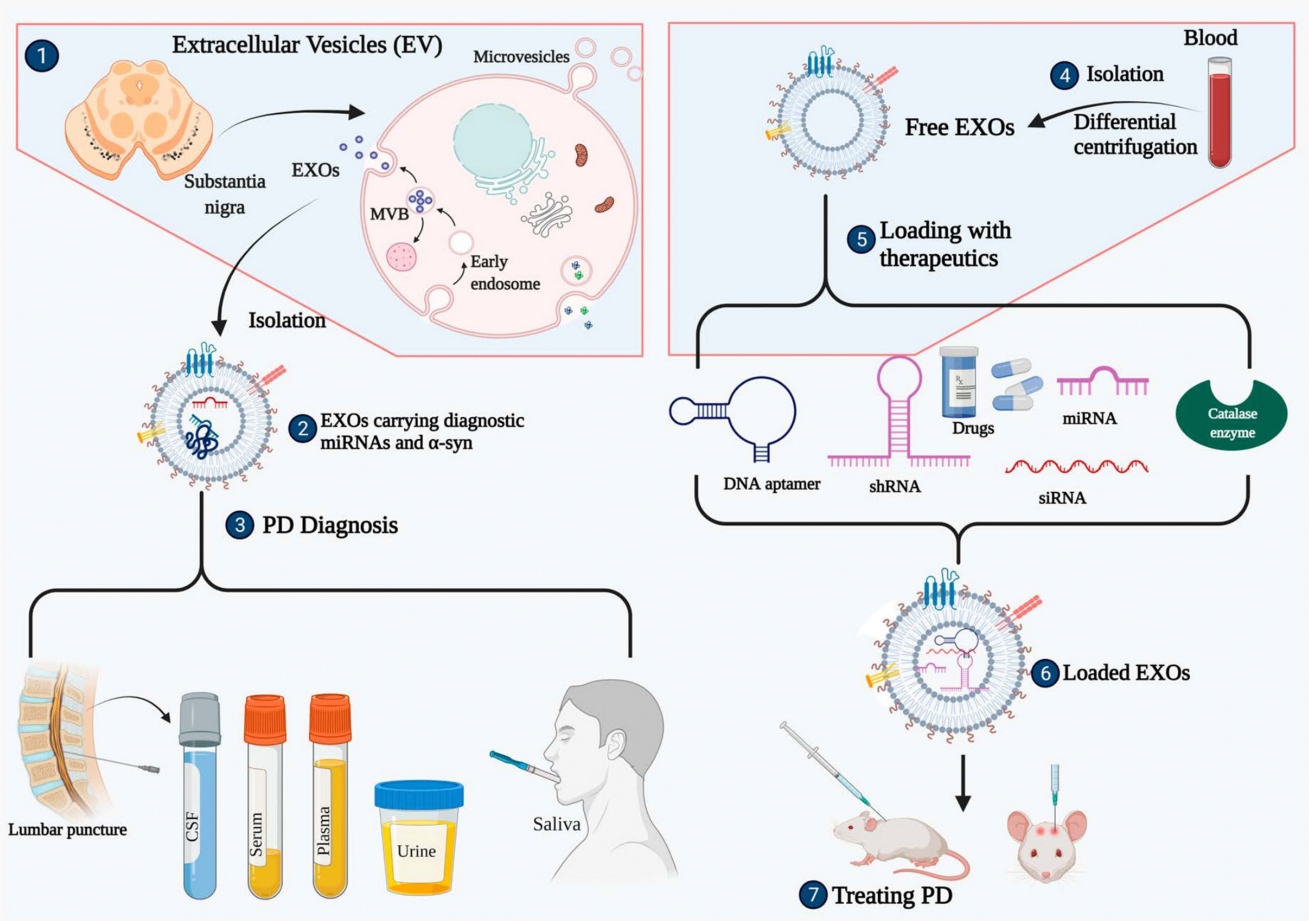

FIGURE 2 Graphical abstract highly the potential of exosomes to be utilized as both diagnostic markers as well as therapeutics for the treatment and management of Parkinson's disease. Research today has investigated the incorporation of various small biomolecules into exosomes owing to their ability to cross the blood–brain barrier. Reprinted with permission from Ouerdane et al.[65]

Furthermore, in a recent study by the same research group, it was shown that naturally produced EVs from oligodendrocyte cultures containing myelin antigens found a decrease in the pathophysiology of experimental autoimmune encephalomyelitis (EAE).[79] In another study, myelin stem cell-derived EVs cocultured with microglia improved myelin healing by recruiting oligodendrocyte precursor cells favoring the recovery of damaged myelin.[80]

A study performed by Williams et al. examined the role of EVs in an EAE model concluded that circulating exosomes exhibit heightened levels during pregnancy.[81] Furthermore, exosomes have been shown to inhibit T-cell activation in an EAE mouse model and aided in the development and migration of oligodendrocyte precursor cells to sites of inflammation.[82] Thus, currently commercially available exosomes derived from placental amnionic fluids may be an excellent avenue of future research for patients with MS.

2.4 | Depression

Depression is a very widespread mental condition that impacts a substantial global population of over 250 million individuals.[83] It may be treated using a wide range of psychological and pharmaceutical techniques, the majority of which involve adjusting the central nervous system's levels of bioenergy amines.[84] Unfortunately, the effectiveness of currently available therapeutic techniques toward managing depression is limited mostly because of their inability to cross the BBB.[85] The pathophysiology of depression is limited by a combination of genetic susceptibility, disrupted monoamine production and function, and altered brain structure and function. Depression is linked to elevated oxidative stress as a result of reactive oxygen species (ROS) production and an imbalance in oxidant and antioxidant signaling.[86] Because of its increased oxygen use, greater lipid content, and more weakened antioxidative defense, the brain is more vulnerable to oxidative stress.[87]

In a paper titled: "Exosomes: A Novel Therapeutic Paradigm for Treatment of Depression", Amanda Silva and colleagues highlighted the potential use of exosomes for the treatment of depressive disorders.[83] Numerous physiological processes, including nerve cell stress, cell-to-cell communication, synaptic plasticity, and neurogenesis, are often seen in the CNS. The ability for exosomes to cross the BBB and transport macromolecules to destination cells is one of their key and unique abilities. The use of exosomes as medicinal

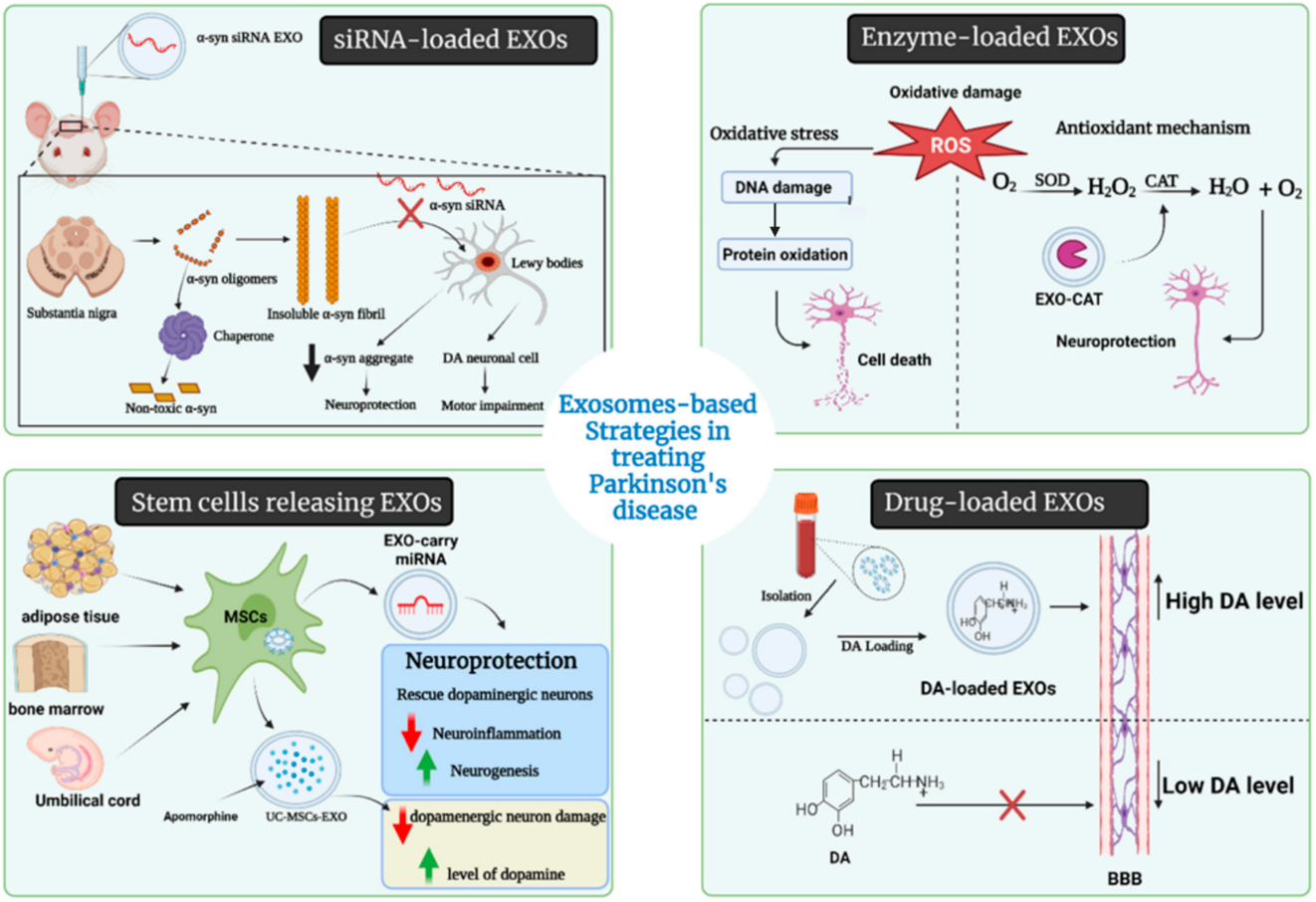

FIGURE 3 Summary of the therapeutic approaches of EXOs in Parkinson's disease. Reprinted with permission from Ouerdane et al.[65]

carriers has been thoroughly investigated in a variety of medical fields, including the treatment of autoimmune diseases and depression will significantly minimize the use of off-target drugs with harmful effects such as antidepressants.

2.5 | Traumatic brain injury

Traumatic brain injury (TBI) affects over 30 million people per year worldwide and caused by a variety of traumatic events including road accidents, falls, exposure to mechanical forces, interpersonal aggression, self-harm, sports injuries, and animal interactions. TBI carries the risk of abrupt or early death in addition to lifelong impairments. Even if the mechanical insult initially results in damage/healing, additional harmful effects are often caused by secondary injury brought on by dysregulated reactions after neuronal death and inflammation. The secretome of MSCs, particularly the exosomes, is primarily responsible for their functional characteristics which have been thoroughly studied as a potential treatment for traumatic brain injury. It has been shown that administering exosomes may improve TBI resulting in a fully recovered brain.[88] The ability to customize MSC-Exos to transport certain biomolecules of interest to improve their therapeutic efficacy is another benefit of recent technological advancements.

MSC therapy of traumatic brain injury in animal models has shown encouraging results. Zhang et al.[89] carried out the oldest known research in 2008 with a cohort of seven patients ranging in age from 6 to 55. In this study, bone marrow-derived MSCs (BMSCs) were administered by two different routes: either directly injected into the lesion or administered intravenously. 6 months later, it was discovered that six individuals had significantly improved their neurological function. Unfortunately, one of the patients had two seizure episodes in the first 2 months and had to go back for regular therapy.[89]

Evidence has suggested that exosomes possess the same or better benefits/advantages when compared to their parent stem cells owing to their ability to cross the BBB, however without the dangers of cell therapies. Because of their anti-neuroinflammatory, angiogenetic, neuroprotective, and neurogenesis qualities, exosomes play a major role in therapy of TBI (Figure 4).

2.6 | Post-traumatic stress disorder

In 1980, post-traumatic stress disorder (PTSD) was officially identified as a mental/anxiety disorder. Since then, a plethora of information on this disorder's symptoms, epidemiology, evaluation, subtypes, and therapy has surfaced.[91] Particularly in military groups,

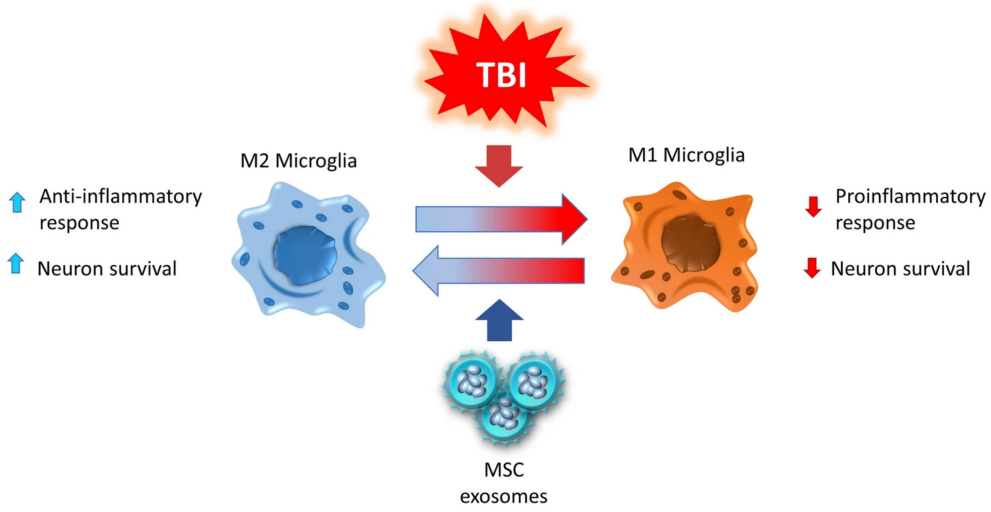

FIGURE 4 Schematic of mesenchymal stromal cell (MSC) exosome polarization of microglia from M1 to M2. MSC exosomes are internalized into trauma activated M1 microglia to promote polarization into M2 state, resulting in secretion of anti-inflammatory cytokines which promote brain repair. Adapted from Li et al.[90] and reprinted with permission from Mot et al.[88]

PTSD is often encountered in conjunction with other mental disorders, traumatic brain injury, and other concomitant symptoms, including depression.[92–94] Moreover, PTSD is associated with a host of other co-morbidities, including hypertension,[95] cardiovascular disease,[96] cardiometabolic diseases,[97] suicidal thoughts,[98] in addition to chronic pain.[99] These highly resemble the disbalance in macrophage polarization toward a pro-inflammatory M1 macrophage phenotype affecting many illnesses. For instance, C-reactive protein (CRP) may indicate PTSD in recently deployed Marines,[100] and cortisol levels in reaction to awakening can predict the outcome of PTSD therapy.[101] While not widely studied in much efficacy, exosomes have been proposed as both an ability to serve as a biomarker in PTSD detection and, more importantly, as a therapeutic alternative to current drug-based therapies for anxiety and PTSD once more knowledge is acquired.[91] Since exosomes are also able to lower inflammation, they may also be infused into the body to lower inflammation as a whole and improve macrophage polarization toward the pro-tissue healing/resolution M2 phenotype (Figure 4).

2.7 | Peripheral nerve injury

The most common type of traumatic damage to the nervous system is peripheral nerve injury (PNI) which affects more than a million individuals yearly.[102] The majority of the time, these injuries lead to permanent impairment, which significantly lowers the patients' quality of life.[103] The peripheral nervous system has the intrinsic capacity to regenerate to a certain extent subsequent to PNI.[104,105] The surgical technique includes end-to-end anastomosis and is widely regarded as the ideal method for repairing peripheral nerves.[106] It is now acknowledged that autologous nerve grafts (ANGs) are the "gold standard" therapy for PNI.[107] Nonetheless, there are still a number of serious problems with the therapeutic use of ANGs, including a lack of donor nerve availability, morbidity at the donor site, the creation of painful neuromas, longer recovery durations, and mismatches in length or diameter.[108,109] Moreover, less than half of the patients who had ANG transplants recovered fully and/or functionally.[110]

Interestingly, exosomes have been shown to have effects on axonal nerve regrowth. A study conducted by Bucan et al.[111] provided evidence that MSC-Exos could stimulate neurite extension in cultured dorsal root ganglion neurons. Furthermore, MSC-Exos have been shown to increase the regeneration process after crush damage to the sciatic nerve in vivo. Research conducted by Zhao et al.[112] showed that BMSC-Exos had a notable impact on enhancing neurite formation and increasing axon length.

Recent research has shown that exosomes may support and regulate the biological activities of Swann cells (SCs).[113] In comparison with the vehicle control group, an in vivo study demonstrated that the exosome-treated group that maximized the functioning of SCs had improved axonal regeneration, remyelination, and muscle repair.[113] It was further shown by Zhang et al.[114] that umbilical cord MSC-derived exosomes improved vascular regeneration by transporting Wnt4 to endothelial cells, where it activated the Wnt/β-catenin pathway. Additionally, it has been shown that exosomes derived from bone marrow and adipose MSCs have pro-angiogenic effects during wound healing.[115,116]

There is a growing body of data suggesting that exosomes have the ability to facilitate vascular regeneration favoring nerve regeneration post-injury. Zhang et al.[117] provided evidence that exosomes derived from MSCs have a substantial impact on promoting angiogenesis in the lesion boundary zone.[117] Consequently, the administration of Immunosomes effectively enhances the recovery of motor function in rats following traumatic brain injury. Figure 5 summarizes the benefits of exosomes for nerve regeneration.

3 | EXOSOMES AND AUTOIMMUNE DISORDERS

The immune system may lead to many illnesses such as heightened inflammation and autoimmune disorders when it becomes overactive. The field of immunomodulation is poised to emerge as a crucial therapeutic approach for the treatment of several disorders owing to the pivotal role played by the immune system in safeguarding the human body.[119,120] Symptoms of an overactive immune system include autoimmune diseases and excess inflammation (Figures 6 and 7). While the body needs some degree of inflammation to defend itself, excessive inflammation may have harmful side effects and impede tissue function at the location of the illness.[121] Autoimmune disorders arise due to the inadequate regulation of effector immune responses against the body's own tissues.[122]

Tregs, or regulatory T cells, are essential for controlling the immune system.[122] Defects in peripheral tolerance, allergy reactions, and eventual autoimmune disorders arise when Treg numbers or function decline. For instance, it has been demonstrated that an increase in TH1-like regulatory T cells is linked with autoimmune disorders.[122] This suggests that in autoimmune disorders, maintaining the regulatory T cell's activity is crucial.[122] Numerous studies have shown that Treg deficits are the root cause of autoimmune disorders such as type 1 diabetes, myasthenia gravis, multiple sclerosis, and rheumatoid arthritis.

Autoimmunity is not only caused by aberrant Treg function. Anti-inflammatory drugs that have the ability to alter inflammatory signals often used to treat inflammation such as nonsteroidal anti-inflammatory medicines (NSAIDs) which block the synthesis of prostaglandins.[123] Extensive research is being devoted toward the investigation of signaling pathway inhibitors,[124] stem cell transplantation,[125] and various other approaches.

3.1 | Exosomes and immune regulation

Prior to discussing the vast roles of exosomes and their therapeutic effects in the management of various autoimmune disorders, it is important to understand how exosomes affect immune cell regulation.[126] Exosomes produced from MSCs transport active signaling molecules and immunomodulatory effectors to control immune cell activity and hence mediate immunological suppression, particularly on T cells and macrophages (Tables 1 and 2). In a study titled: "Immunosuppressive Effects of Mesenchymal Stem Cells-derived Exosomes,"[127] MSC-Exos were clearly shown to regulate immune responses by interacting with immune effector cells. Both physical and chemical factors were shown to affect MSC-Exos.[127]

Lipid molecules found in abundance in MSC exosome membranes may merge with target cells to convey cargoes.[150] The transfer and presentation of antigen peptides, the transport of miRNA, the DNA-driven cyclic GMP-AMP synthase stimulator of interferon genes in recipient cells, and other signaling pathways produced by surface-carrying ligands are possible causes of the immunoregulatory actions of MSC-Exos.[151] MSC-Exos suppress immune cell activation and encourage the production of anti-inflammatory molecules, which lessens inflammatory reactions.[152–154]

MSC-Exos have the ability to modulate immune cells when they are prompted to become active. For instance, when T cells are stimulated by antigen-presenting cells, MSC-Exos may convert T cells into Tregs.[154–156] MSC-Exos, like their parent MSCs, also have an immunosuppressive effect. Crucially, pretreatment may regulate the specificity and immunosuppressive effects of MSC-Exos. For example, MSC-Exos that are treated with a high concentration of pro-inflammatory substances have higher immunosuppressive effects. MSC-Exos have the ability to migrate to the site of injury and impede the immune system. MSC-Exos are injected into the body, and their purpose is to reduce inflammation by migrating to the immune organs, inflammatory tissues, and injured areas. After being injected intravenously, MSC-Exos may be administered to the sites of damage, ingested by immune cells, and found in the spleen and $CD260^{+}$ cells 24 h later.[157] In the past 2 years alone, there are dozens of systematic reviews that have investigated the role of exosomes in autoimmune disorders (Figure 8).[158–167]

3.2 | Allergy

An increasingly significant worldwide health and economic burden is caused by allergic reactions and disorders. The search for new therapeutic strategies is necessary since there are no disease-modifying treatments other than particular allergen immunotherapy (AIT), which is not available for all allergy types.[168] A lack of immunological tolerance and the expansion of TH2 cells, which activate B cells to generate IgE responses in response to benign antigens, characterize type I hypersensitivity.[169,170] Because allergen-specific IgE binds to the high-affinity IgE receptor Fc"RI, it sensitizes mast cells and basophils.[171] Upon secondary contact with the allergen, those cells degrade and release inflammatory mediators.[172] Symptomatic treatment options for allergies involve downregulation of the mediators released by mast cells or basophils (e.g., anti-histamine) or aim to downregulate IgE levels, such as the monoclonal anti-IgE antibody Omalizumab.[173]

EVs significantly contribute to the shaping of immune responses in both physiology and disease states. While vesicles secreted by immune cells are often implicated in the allergic process, growing evidence indicates that EVs from nonimmune cells produced in the stroma or epithelia of the organs directly affected by inflammation may also play a significant role. An overview of the mechanisms of allergy to which those EVs contribute, with a particular focus on exosomes is presented in Figure 9.[174]

Recent progress in the EV field determined that a thorough understanding of EV biology and function is pivotal for the comprehension of immune-driven diseases, including the pathogenesis of allergy. EVs contribute to asthma pathogenesis via various mechanisms related to both inflammation and pathological remodeling,[175] and there are interesting interdependencies that have been

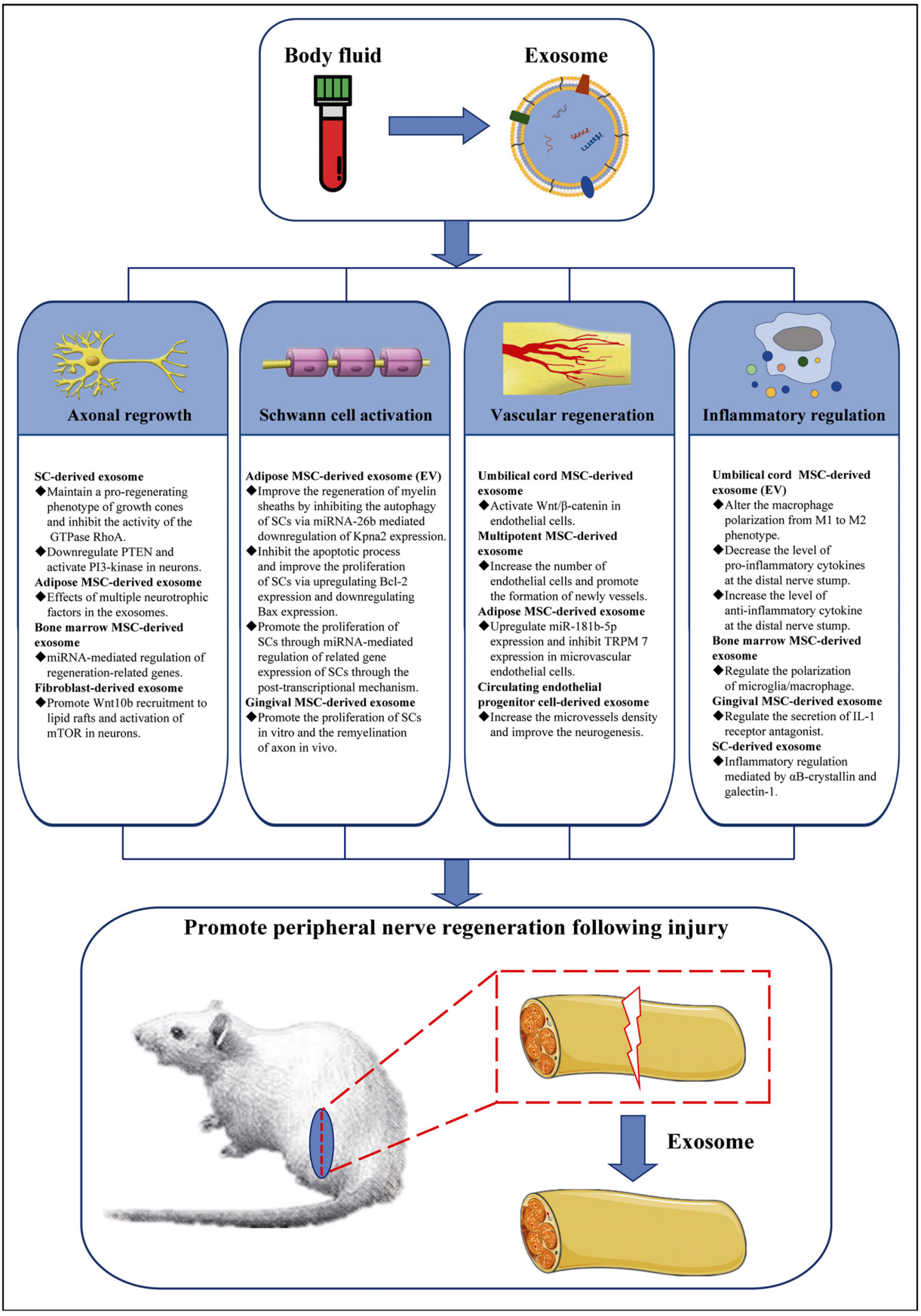

FIGURE 5 Effects of exosomes on peripheral nerve regeneration. Exosomes can exert therapeutic effects via mediating axonal regrowth, Schwann cell activation, vascular regeneration, and inflammatory regulation, which contribute to providing a favorable microenvironment for peripheral nerve regeneration. Reprinted with permission from Yu et al.[118]

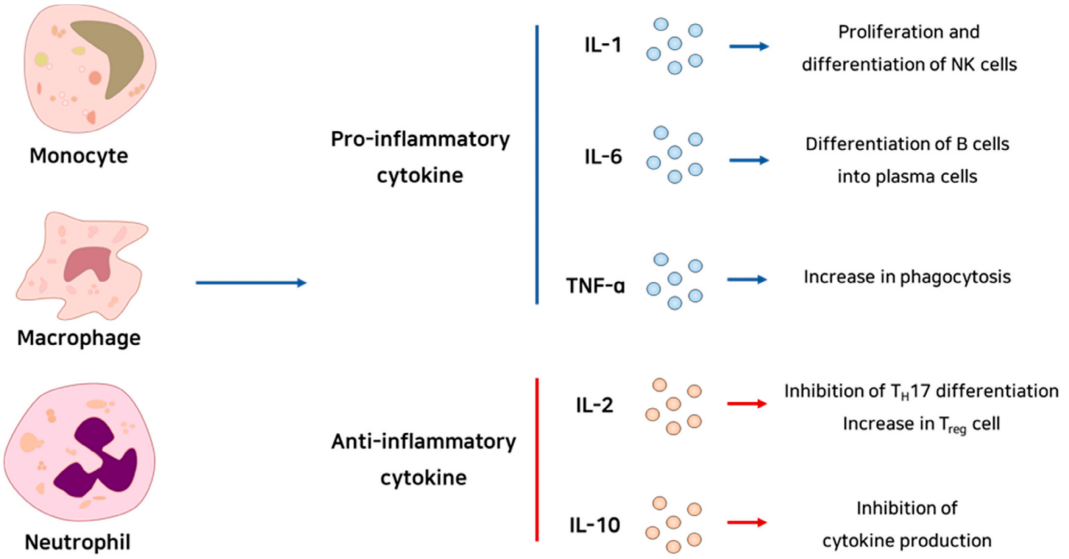

FIGURE 6 Schematic summary of immunoregulatory cells and cytokines. Reprinted with permission from Suh et al.[120]

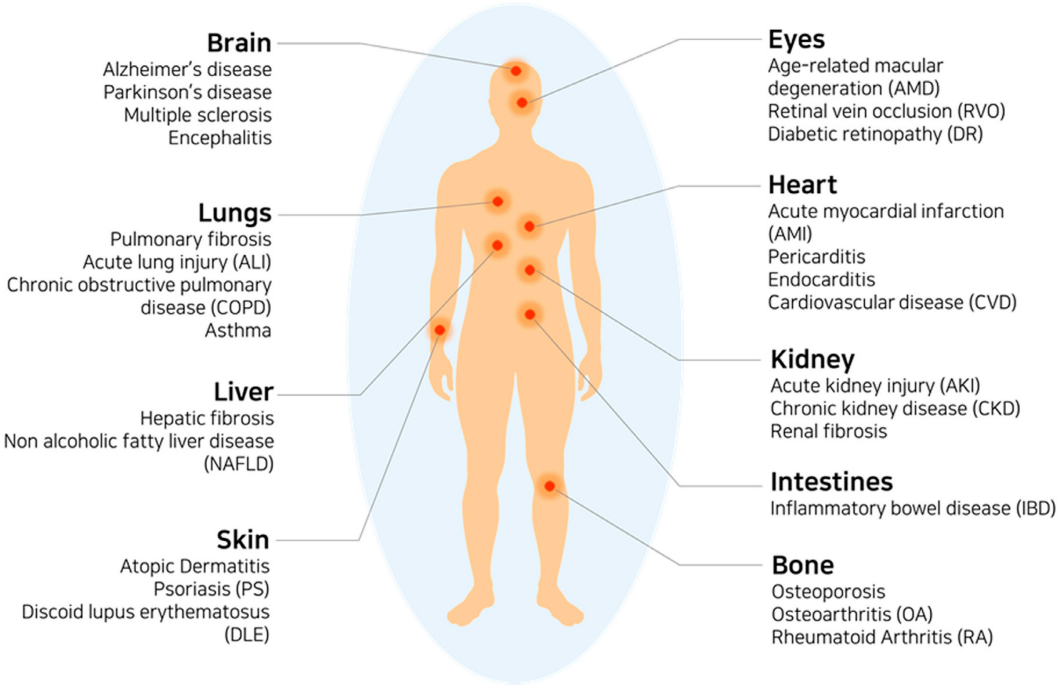

FIGURE 7 Schematic of the human body with inflammatory diseases. Reprinted with permission from Suh et al.[120]

observed. Specifically, it has been shown that fibroblast-derived EVs secreted by cells obtained from severe asthmatics increase the proliferation of bronchial epithelial cells in comparison to those in healthy individuals due to a decrease in the TGF-b2 content.[176] Vice versa, vesicular transfer between epithelial cells and fibroblasts which includes inositol polyphosphate 4-phosphatase type I A (INPP4A) cargo, may regulate inflammation and airway remodeling.[177] Furthermore, Gupta et al. demonstrated that sEV transfer between airway epithelial cells and human tracheobronchial cells promotes the expression of several proteins which may contribute to allergic inflammation and exacerbation of asthma symptoms, that is, gel-forming mucins.[178] The addition of an allergen source (house dust mite) to the airway epithelial cells culture resulted in DC activation by secreted EVs in vitro and increased airway inflammation in a murine model.[179] While the goal of this overview review article is not to specifically provide major input on the role of exosomes in allergy, a recent review article[174] on this topic has greatly demonstrated all the preclinical animal studies (Table 3) and clinical studies (Table 4), currently underway highlighting the prolific role of small vesicles for the management/treatment of allergic diseases.

Furthermore, various groups have elicited various roles of exosomes in allergic sensitization and inflammation and further discuss

TABLE 1 miRNA involved in the immunosuppressive effects of mesenchymal stromal cell exosomes on macrophages cells.

miRNA	Mechanism	Effect	References
miR-let-7b	Negatively regulated TLR4 and p-p65 expression, suppressed STAT3 and AKT phosphorylation	Orchestrated macrophages plasticity	128
miR-let-7c	–	Downregulated MMP9, TGF-β1	129
miR-145	Inhibited the expression of MRP1	Promoted phagocytic activity of macrophages	130,131
miR-146a	Inhibited the expression of TRAF6 and IRAK1, reduced phosphorylation of NF-κB-p65 and IκBα	Reduced the production of pro-inflammatory factors in macrophages	132
miR-146b	Lessened the release of pro-inflammatory factors and the pro-inflammatory response by NF-κB	Improved the survival rate of sepsis mice	133
miR-17	Inhibited the activation of NLRP3 inflammatory bodies in macrophages by targeting TXNIP	Reduced the levels of pro-inflammatory factors IL-1β and IL-18 and improved ALF	134
miR-181c	Reduced TLR4 expression	Reduced pro-inflammatory response in macrophages	135
miR-223	–	Inhibited the expression of TNF-α, IL-1β, and IL-6 in sepsis-induced macrophages	136
miR-455-3p	Through combination of miR-455-3p and 3′UTR site of PIK3R1 gene	Reduced macrophages infiltration and the secretion of pro-inflammatory factors	137
lncRNA KLF3AS1	Downregulated MMP13 expression	Inhibited chondrocyte apoptosis	138

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TABLE 2 miRNA involved in the immunosuppressive effects of mesenchymal stromal cell exosomes on T cells.

miRNA	Mechanism	Effect	References
miR-1246	Regulated the IL-6-gp 130-STAT3 pathway	Reduced the Th17/Tregs ratio in $CD4^+$ T cells and improved liver dysfunction	139
miR-125a-3p	–	Inhibited the activation of $CD3^+$ T cells and promoted the Tregs populations	140
miR-126	Reduced NLRP3 inflammatory body activity and NF-κB-p65 levels	Improved retinal inflammation which caused by hyperglycemia	141
miR-1470	Targeted c-jun mRNA 3′ region	Inhibited c-jun expression and promoted the upregulation of P27KIP1 and the ratio of $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs	142
miR-17	Inhibited the transactivation of Jak1	Reduced IL-7 signal transduction and the production of pro-inflammatory factors	143
miR-17-92	Negatively regulated PTEN expression and activated the PI3k/Akt/mTOR signaling pathway and inhibited GSK-3β activity	–	144
miR-181a	Downregulated c-Fos protein expression the expression of TGF-β and IL-6 and the expression of Foxp3	Improved the area of cerebral infarction and lessened inflammatory infiltration and effectively reduced myocardial I/R damage	145
miR-221	Targeted TIMP2	Reduced the expression of PTEN and p27 proteins, accelerated the proliferation, migration, and invasiveness of GC cells	146
miR-223-3p	Negatively regulated STAT3	Inhibited the secretion of IL-17 by Th17 cells and reduced the expression of IL-1β and IL-6, increased the ratio of Tregs/Th17	147
miR-29b-3p	Downregulated PTEN	Activated the Akt signaling pathway	148
miR-92a-3p	Inhibited Wnt	Regulated T cells development	149

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the mechanisms by which exosomes could potentially be used in immunotherapeutic approaches for the treatment of allergic diseases. For an excellent review article on the topic by Engeroff and Vogel,[168] the following four strategies have been proposed as potential for utilizing exosomes in the field of allergy:

- Exosomes generated from mast cells that express the IgE receptor Fc"RI have the ability to absorb IgE and reduce systemic IgE levels.
- Tolerogenic exosomes have the potential to inhibit allergic reactions by stimulating regulatory T cells.

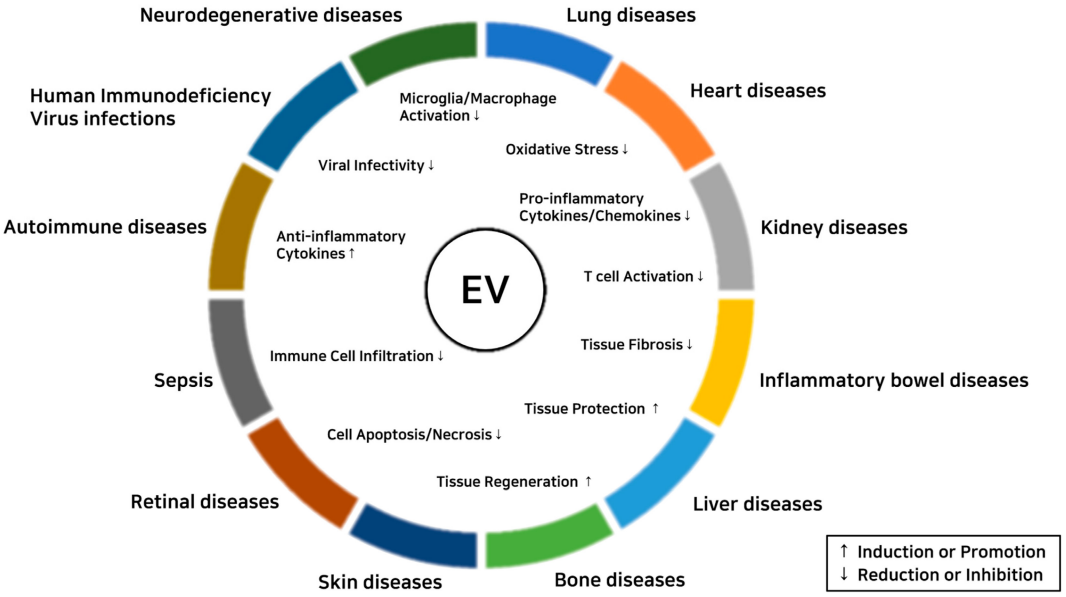
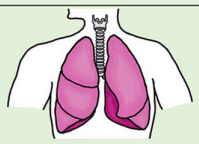
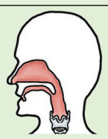
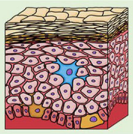
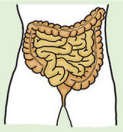
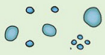
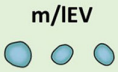


FIGURE 8 Therapeutic effects of extracellular vesicles (EV) on inflammatory diseases. Reprinted with permission from Suh et al.[120]

EXTRACELLULAR VESICLES	EV SOURCE vs. EFFECT ON ALLERGIC INFLAMMATION			
				
	Asthma	Allergic rhinitis	Atopic dermatitis Contact dermatitis	Allergic GI disorders Food allergy
sEV 	+ HBECs → neutrophilic inflammation ↑ → monocyte chemotaxis ↑ → Th2 differentiation ↑ → DC maturation ↑ + BALF → proinflammatory response ↑ → leukotriens ↑ + FBs → HBECs proliferation ↑ + AECs → HTBEs: mucus production and inflammation ↑ + AECs → DC activation ↑ + AECs → Th2 bias via IL-33 ↑ - MSCs → ILC2 accumulation ↓ → immune infiltration ↓ → Th2 cytokines ↓ → mucus production ↓ - HBECs → airway remodelling ↓ - AECs → Treg induction ↑	+ NM → Th2 inflammation ↑ - NECs → IL-10+ monocytes ↑	+ KCs → DC activation ↑ - MSCs → IgE levels ↓ → blood eosinophils ↓ → mast cell infiltration ↓ → Th2/proinflammatory cytokines ↓ → epidermal barrier function ↑ → tissue damage ↓ - RBCs → delayed hypersensitivity ↓ → T cell activation ↓ - MSC → contact hypersensitivity ↓ → Tc, Th1 activation ↓ → Treg induction ↑	- IECs → Treg induction ↑ → IL-10 production ↑ → T cell proliferation ↑
m/lEV 	+ HBECs → macrophage inflammation ↑			

+ disease promoting effect; - disease alleviating effect; ↑ increase in a process; ↓ decrease in a process

FIGURE 9 Extracellular vesicles produced by nonimmune cells and their involvement in allergic diseases. Microvesicles and exosomes are the two types of extracellular vesicles, which have been implicated in the pathogenesis of allergic inflammation. There is significant predominance of the exosomal involvement, likely due to the phenotypic characteristics and physical properties of these vesicles, enabling more without damage and entering the circulation for long-distance delivery. Reprinted with permission by Hovhannisyan et al.[174]

TABLE 3 Preclinical models using EVs for allergy treatment in animals.

Study title	Conditions	Outcomes	References
Exosomes from bronchoalveolar fluid of tolerized mice prevent allergic reaction	Allergy	BALF-derived exosomes induce tolerance and protection against allergic sensitization in mice	Prado et al.[180]
Pro-inflammatory role of epithelial cell-derived exosomes in allergic airway inflammation	Asthmatic inflammation	IL-13 treated epithelial cell-derived exosomes induce enhanced proliferation and chemotaxis of undifferentiated macrophages in the lungs during asthmatic inflammatory conditions	Kulshreshtha et al.[181]
Selective release of miRNAs via extracellular vesicles is associated with house dust mite allergen-induced airway inflammation	Allergic airway inflammation	Selective sorting of Th2 inhibitory miRNAs into airway secreted EVs and increase release to the airway is involved in the pathogenesis of allergic airway inflammation	Gon et al.[182]
Exosomes derived from human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis	Atopic dermatitis	Intravenously or subcutaneously injected human adipose tissue-derived MSC-Exos ameliorate AD in an in vivo mouse model	Cho et al.[183]
Extracellular vesicles from mesenchymal stem cells prevent contact hypersensitivity through the suppression of Tc1 and Th1 cells and expansion of regulatory T cells	Allergic contact dermatitis	Human umbilical cord-derived MSC-EVs prevent the pathology of contact hypersensitivity by inhibiting Tc1 and Th1 immune responses and inducing the Tregs phenotype in vivo and in vitro	Guo et al.[184]
Small extracellular vesicles derived from human mesenchymal stromal cells prevent group 2 innate lymphoid cell-dominant allergic airway inflammation through delivery of miR-146a-5p	Allergic rhinitis (patients) ILC2-dominant asthma (mouse model)	MSC-sEVs prevent ILC2-dominant allergic airway inflammation through miR-146a-5p	Fang et al.[185]
Exosomes from human adipose tissue-derived mesenchymal stem cells promote epidermal barrier repair by inducing de novo synthesis of ceramides in atopic dermatitis	Atopic dermatitis	Human adipose tissue-derived MSC-Exos effectively repair defective epidermal barrier functions in atopic dermatitis	Shin et al.[186]
Syngeneic red blood cell-induced extracellular vesicles suppress delayed-type hypersensitivity to self-antigens in mice	Delayed-type hypersensitivity contact hypersensitivity	Intravenous delivery of syngeneic mouse red blood cells that is mediated by EVs in a miRNA-150-dependent manner suppresses delayed-type hypersensitivity	Nazimek et al.[187]
Intranasal delivery of MSC-Exos attenuates allergic asthma via expanding IL-10 producing lung interstitial macrophages in mice	Allergic asthma	Intranasally delivered MSC-Exos inhibit allergic asthma in mice	Ren et al.[188]
Epithelial exosomal contactin-1 promotes monocyte-derived dendritic cell–dominant T-cell responses in asthma	Airway allergic models asthma	Epithelial contactin-1 in exosomes is a critical player in asthma pathology	Zhang et al.[179]

Note: Reprinted with permission by Hovhannisyan et al.[174]

- Exosomes may encourage TH1-like reactions in response to an allergen.
- Exosomes may alter how IgE facilitates the presentation of antigens.[168]

HBECs, human bronchial epithelial cells; BALF, bronchoalveolar lavage fluid; NM, nasal mucus; NECs, nasal epithelial cells; AECs, airway epithelial cells; HTBEs, human tracheobronchial cells; RBCs, red blood cells; IECs, intestinal epithelial cells; KCs, keratinocytes; FBs,

TABLE 4 Registered clinical trial investigating the feasibility of using EVs in allergic patients.

Study title	Conditions	Interventions	Locations	Identifier
Non-coding RNAs analysis of eosinophil subtypes in asthma	Allergic asthma, severe eosinophilic asthma	Biological: Dermatophagoides pteronyssinus allergen Procedure: Blood sampling, Procedure: Bronchial challenge with allergen	Lithuanian University of Health Sciences, Pulmonology Department Kaunas, Lithuania	NCT04542902
Effectiveness of Qufeng Shengshi Fang on treatment of allergic rhinitis	Rhinitis, allergic, perennial	Drug: Qufeng Shengshi Fang and Loratadine, Drug: Loratadine	Peking Union Medical College Hospital Traditional Chinese medicine department Beijing, Beijing, China	NCT02653339
Cohort study of the patterns of microvesicles in the serum of participants with Atopic and non-atopic asthma	Asthma, allergies	Biological: tumor derived microparticles, Drug: cisplatin	The Ohio State University Medical Center Columbus, Ohio, United States	NCT00700726
Influence on human bronchial epithelial cells smoker extracellular vesicles influence on human bronchial epithelial cells	Smokers human bronchial epithelial cells lung pathogenesis biomarkers	Diagnostic test: Bronchoalveolar lavages	Hôpital Saint-Philibert, Lomme, France	NCT03608293
Phase I/IIa study on chitin microparticles in subjects suffering from allergic rhinitis	Seasonal allergic rhinitis	Drug: Chitin microparticles by nasal route	Hammersmith Medicines Research, London, United Kingdom	NCT00443495
Exploratory study of the cutaneous penetration of biodegradable polymeric Microparticles in atopic dermatitis (MicroIskin)	Atopic dermatitis	Drug: Biodegradable and biocompatible polymeric microparticles containing a fluorochrome applied to the skin followed by a skin biopsy	Regional University Hospital Besançon, France	NCT02369432
Impact of narrowband UVB phototherapy on systemic inflammation in patients with atopic dermatitis	Atopic dermatitis	Other: Narrow band UVB treatment (NB-UVB)	The Rockefeller University New York, New York, United States	NCT03083730
Trial on vascular inflammation in atopic dermatitis	Atopic dermatitis vascular inflammation coronary atherosclerosis	Other: FDG-PET scan other: MDCT, other: biopsy and blood collection	Innovaderm Research Inc Montreal, Quebec, Canada	NCT02926807
Role of macrophage in immune modulation by mesenchymal stem cell derived exosome in asthma	Respiratory disease	Primary indicator: PD-L1, immunosuppression capacity of regulatory T cell	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University	ChiCTR2000031122

Note: Reprinted with permission by Hovhannisyan et al.[174]

fibroblasts; MSCs, mesenchymal stem cells. ↑ increase in a process; ↓ decrease in a process; + disease promoting effect; − disease alleviating effect. Reprinted with permission.[174]

3.3 | Atopic dermatitis and contact allergy

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is characterized by severe pruritus, eczematous cutaneous lesions, and disruption of the epidermal barrier. The pathophysiology of AD is multifaceted, with Th2 cells and ILC2 being the primary mediators of cytokine production.[189] Innate, Th17, and Th22 components are also involved.[190] However, delayed-type hypersensitivity to minor contact allergens, such as contact allergy and contact sensitization, is rather prevalent. An allergy to anything touched repeatedly or for extended periods of time is called contact dermatitis.[191–193] The study conducted by Nazimek et al. demonstrates that the introduction of syngeneic mouse red blood cells through intravenous administration results in the generation of EVs. These EVs exhibit the ability to inhibit the immune response known as directed delayed-type hypersensitivity, and this effect was shown to be dependent on the presence of miRNA-150. More specifically, the EVs derived

from syngeneic mouse red blood cells reduce the activation of T cells and promote their programmed cell death.[187] Similarly, it has been shown that EVs generated from human umbilical cord MSCs may both prevent and treat the pathophysiology of touch hypersensitivity in mice.[184] In particular, these EVs suppressed the production of TNF-a and IFN-g, induced Tregs, and decreased the amount of released IL-10 in both $CD8^+$ cytotoxic cells and $CD4^+$ Th1 cells.[184] While this field remains in its infancy in terms of clinical applicability, future understanding of exosomes, including their ability to modulate the immune system, should shed light on potential avenues of future uses of exosomes for the treatment of AD and contact allergy.

3.4 | Lupus

Systemic lupus erythematosus (SLE) is a common autoimmune connective tissue disease with unclear etiology and pathogenesis. It is characterized by the excessive synthesis of pathogenic autoantibodies and immunological complexes, aberrant immune cell activation, and organ-wide effects.[194] The immunological problems that accompany the complicated etiology and pathophysiology of SLE include aberrant T cell, mononuclear macrophage cell, and B cell growth, differentiation, activation, and malfunction. Chronic inflammatory conditions and autoimmune diseases ultimately lead to harm to tissues and organs.[195,196]

The most frequent and serious organ impairment in SLE is lupus nephritis.[197] Currently, SLE is conventionally treated with glucocorticoids and immunosuppressants. Nevertheless, a significant number of patients with refractory conditions continue to present challenges in achieving clinical remission, resulting in elevated death rates. SLE patients have significant economic and psychological challenges.[198] Therefore, there is still a pressing need to develop solutions to the issue for SLE patients.

In a paper by Yang et al. titled: "Immunomodulatory Effect of MSCs and MSCs-Evs in Systemic Lupus Erythematosus"[199] it has been shown that MSCs and the exosomes they produce are useful in controlling innate and adaptive immunity, which are engaged in a variety of pathological and physiological processes and support immunological homeostasis in sickle cell disease.[199] Figure 10 gives new insight into the pathophysiology of SLE and directs biological

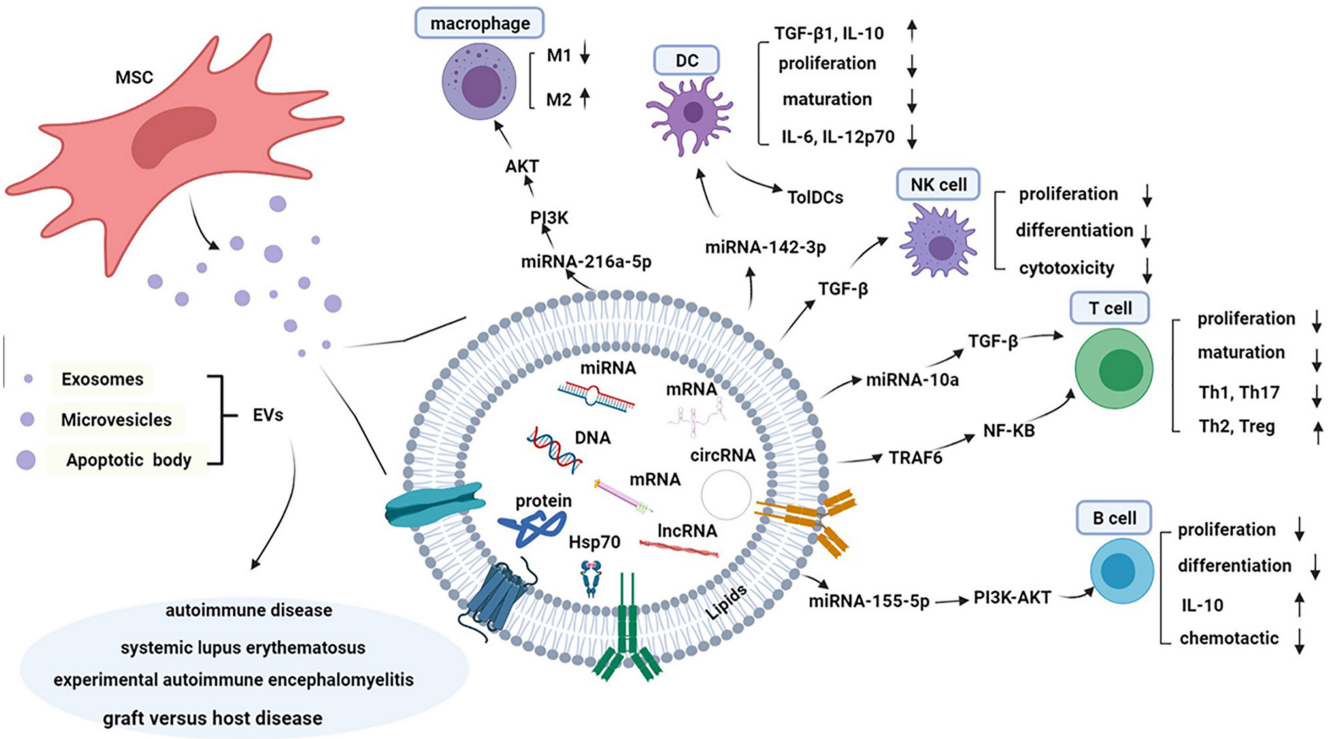


FIGURE 10 Composition and mechanism of immunological tolerance of MSC-EVs in systemic lupus erythematosus. MSC-EVs are spheroidal shaped and two-layer lipid particles containing various types of protein, lipids, DNAs, non-coding RNAs, miRNAs, and mRNA, which cause genetic information exchange by various of signal pathway and reprogramming of the recipient cell. MSC-EVs can suppress the differentiation and proliferation of B cell by PI3K-AKT pathway and reduce production of IL-10. Similarly, T cells play the suspensive role on the proliferation and maturation, while reducing the production of Th17 and Th1 and improve function of Treg and Th2 through the TGF-b/NF-kB pathway. EVs can suppress the proliferation and maturation of DCs and induce tolerable DCs with low expression of costimulatory makers. Macrophages can transform to anti-inflammatory M2 phenotype after treating by MSC-EVs through the PI3K/AKT pathway. EVs can suppress the proliferation, differentiation, and cytotoxicity of NK cells in a TGF-b-dependent manner. MSC-EVs play an important role in the pathogenesis of autoimmune diseases, including SLE, graft-versus-host disease, and experimental autoimmune encephalomyelitis. Reprinted with permission from Yang et al.[199]

treatment by illuminating all the underlying mechanisms and immunomodulatory effects of MSC/MSC-EVs in SLE.[199]

3.5 | Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes cartilage and bone damage with a considerably high social and economic impact. Severe systemic consequences, including cardiovascular events, as well as lifelong disability and function loss, are all possible outcomes of RA. The most frequent symptoms are related to symmetrical knee, foot, wrist, and hand discomfort and edema.[200] Approximately 0.5%–1% of the global population is affected with RA, which may affect people of any age, but it is most common in those in their third, fourth, and fifth decades.[201] Even if disease remission may be achieved with strict management and treat-to-target tactics, as recommended by current guidelines, RA is still regarded as an incurable condition.[201] More than half of patients have disease flares, which significantly increase the risk of radiographic damage, worse quality of life, disability, use of healthcare services, and expenses.[202,203] At present, there are no markers for tailored treatment or predictors of therapeutic response. However, RA causes irreparable damage to joints or organs as well as persistent inflammation if treatment is not received. Therefore, the most prevalent symptoms in RA patients are increased disability and shorter lifetime.[204,205]

Bone marrow mesenchymal stem cells (BMSCs) were tested originally and demonstrated significant improvements in symptoms of refractory patients in two clinical studies.[206,207] These outcomes are in line with the majority of BMSC-based arthritic models. Consequently, BMSC-derived exosomes (BMSC-Exos) have been suggested as a potential treatment for RA because they have effects similar to those of their parent MSCs without compromising the immune system.[208]

The function of BMSC-Exos in RA models was first studied by Stella et al. who demonstrated that these Exos prevented T and B lymphocyte proliferation and generated Treg and IL-10-expressing regulatory B cells dose-dependently to mitigate experimental RA.[208] The immunomodulatory properties of BMSC-EVs have shown positive outcomes in various animal models of osteoarthritis.[209,210] Moreover, BMSC-EVs have been shown to contribute to angiogenesis and bone/cartilage regeneration.[209,211]

The primary mechanism by which MSC-EVs affects the illness is by the transfer of miRNAs,[212] thus inhibiting the cyclin I/ATM/ATR/p53 signaling pathway.[213] In addition, EVs were shown to overexpress a number of miRNAs that were previously downregulated in synovial tissue but were effective in treating inflammatory arthritis. One of them, miR-192-5p, regulates the immunological response by targeting Ras-related C3 botulinum toxin substrate 2, therefore delaying the inflammatory response in rat models of collagen-induced arthritis.[214] It was shown that miR-320, which is secreted from BMSCs via exosomes, selectively downregulates the chemokine ligand CXCL9, hence preventing RA-FLS activation, migration, and invasion.[215] Matrix metalloproteinase 14 and vascular endothelial growth factor (VEGF) are two proteins involved in angiogenesis that are downregulated by exosomal miR-150-5p.[216,217]

Although BMSC-EVs have a beneficial impact on RA, the mechanisms by which they enhance immune modulation and anti-inflammatory responses in RA remain poorly understood and hence need more study. Additionally, umbilical cord mesenchymal stem cells and EVs produced from AMSCs (AMSC-EVs)[218] have been proposed as a therapy for RA.[219,220] Figure 11 highlights various mechanisms by which MSC-Evs impact RA.

3.6 | Osteoarthritis

Osteoarthritis (OA) is a long-term degenerative joint disease that is characterized by synovial inflammation, subchondral bone sclerosis, articular cartilage deterioration, and the growth of osteophytes.[158,222] Joint pain, swelling, and abnormalities are the primary clinical signs. The loss of articular cartilage is the primary degenerative alteration.[223] Joint pain is brought on by dysfunction, but it also has an impact on the patient's quality of life and ability to sleep.[224]

A recently filed clinical study (NCT05060107) aims to provide MSC-Exos intravenously for the purpose of managing OA. A total of 10 participants were enrolled in a Phase 1 clinical study and thereafter monitored for duration of up to 12 months in order to validate the safety of MSC-Exos as a therapeutic intervention for OA.

Many preclinical studies exist supporting the use of exosomes. A study conducted by Zhang et al.[225] revealed that the use of chitosan hydrogels as carriers loaded with MSC-Exos had the potential to enhance the stability of proteins and miRNAs inside MSC-Exos. Liu et al. conducted a study in which they incorporated MSC-Exos into a hydrogel glue using the photoinduced imine crosslinking (PIC) technique. These results suggested that the MSC-Exos is a promising strategy for treating articular cartilage abnormalities since it may stimulate repair and regeneration of damaged cartilage.[226]

Additionally, anti-inflammatory molecules with low bioavailability such as curcumin may also be encapsulated using MSC-Exos as carriers. Consequently, curcumin has been loaded into MSC-Exos as a drug delivery system for curcumin at the nanoscale. The phosphorylation of p-38MAPK and Erk1/2, PI3K/Akt, caused by IL-1β may be reduced by curcumin-encapsulated MSC-Exos, which in turn reduces the activity of pathways involving these kinases.[227] Accordingly, the curcumin-encapsulated MSC-Exos may also cause target cells to express miR-126-3p more highly and lessen the IL-1β-induced OA chondrocyte breakdown.[227] While the therapeutic benefits of MSC-Exos have shown promise in both clinical and animal settings, it is essential to further increase research to elucidate the underlying mechanism and ensure the safety of MSC-Exos prior to their widespread clinical use.

The chondroprotective and anti-inflammatory effects of murine BMSC-Exos have been demonstrated in the treatment of a mouse model of collagenase-induced osteoarthritis (CIOA).[158] These effects were achieved by (1) restoring the homeostatic state of

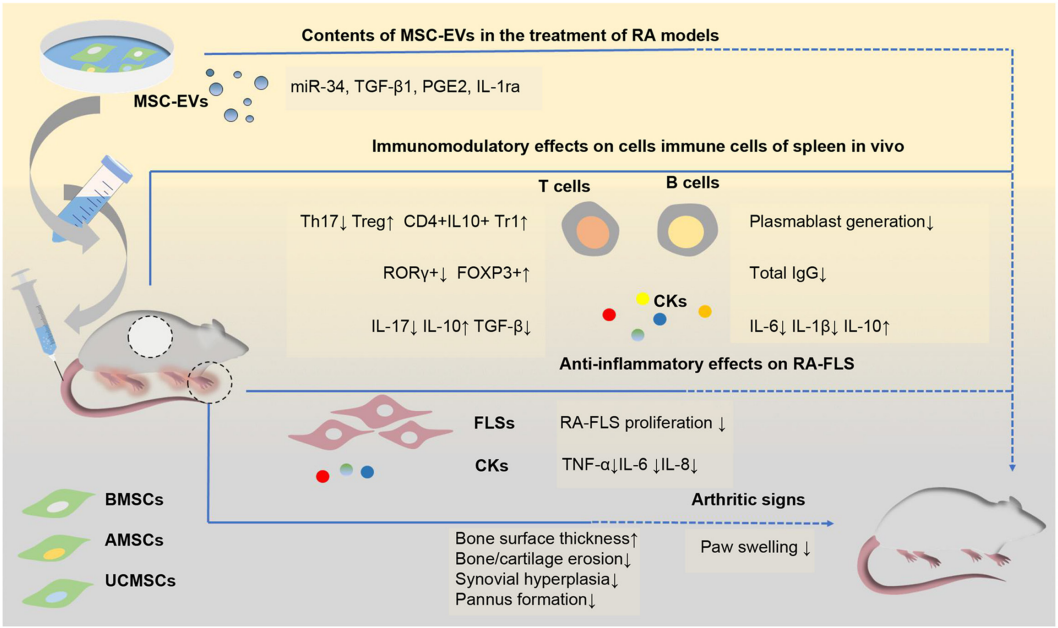


FIGURE 11 Schematic view of the potential mechanisms of mesenchymal stem cell-derived EVs in the treatments of rodent models of RA. EVs from different sources of MSCs show efficacy in the treatment of RA models. These EVs mainly show the immunosuppressive function of inhibiting T-cell proliferation, downregulating Ig production and decreasing pro-inflammatory factors levels in vivo, thus attenuating clinical signs of paw swelling as well as histopathological indicators of bone and cartilage erosion and pannus formation. Several contents (including miR-34, TGF-β1, and IL-1ra) have been indicated to be associated with these functions. AMSC-EVs, adipose tissue mesenchymal stem cell-derived extracellular vesicles; BMSC-EVs, bone marrow mesenchymal stem cell-derived extracellular vesicles; CKs, cytokines; FLS, fibroblast-like synovial cells; FOXP3: fork-head box protein P3; Ig, immunoglobulin; IL, interleukin; IL-1ra, IL-1 receptor antagonist; miR-34, microRNA-34; MSC-EVs, mesenchymal stem cell-derived extracellular vesicles; PGE2, prostaglandin E2; RA, rheumatoid arthritis; ROR-γ, retinoic acid receptor-related orphan receptor γ; TGF-β: tumor growth factor beta; Th17, T helper 17; TNF-α, tumor necrosis factor alpha; Tr1, T regulatory type-1; Treg, regulatory T cells; UC-MSC-EVs, umbilical cord mesenchymal stem cell-derived extracellular vesicles. Reprinted with permission from Miao et al.[221]

chondrocytes, (2) preventing chondrocyte apoptosis, and (3) promoting a shift in macrophages toward an anti-inflammatory phenotype.[210] Furthermore, by switching synovial macrophages from M1 to M2 and minimizing the breakdown of articular cartilage, a recent study showed that intra-articular injection of BMSC-Exos might reduce OA damage in rat models.[209] In vitro TNF-alpha-stimulated OA, BMSC-EVs have also been suggested to enhance cartilage regeneration and exhibit anti-inflammatory properties.[228] Zhu et al.[229] also demonstrated that by promoting chondrocyte migration and proliferation, transplanting-induced pluripotent stem cell-derived MSC-Exos had a significant therapeutic benefit in the CIOA animal model when compared to MSC-Exos obtained from synovial membranes.

Overexpression of miR-140-5p in MSC-Exos has also been shown to promote cartilage tissue regeneration and reduce knee joint damage in a rat model of osteoarthritis.[230] It has recently been shown that LPS-primed MSC-EVs promote knee cartilage healing in an OA animal model by increasing chondrocyte proliferation, migration, and decreasing apoptosis.[231] Wang et al.[232] showed that in a mouse model of OA, MSC-Exo-miR-155-5p increased chondrocyte proliferation and migration, decreased apoptosis, modulated production of cartilage ECM, that resulted in a final increase in cartilage regeneration. By restoring a healthy equilibrium between ECM production and degradation, intra-articular infusion of embryonic stem cell (ESC)-MSC-Exos alleviated cartilage injury and decreased matrix degradation in a mouse model of medial meniscus instability.[233] In addition, BMSC-Exos alleviated knee discomfort in arthritic rats and had regenerative effects on cartilage damage and ECM synthesis.[234] Recent research by Jin et al.[235] discovered that miR-26a-5p in particular, which is produced in BMSC-Exos, may reduce OA damage in vivo by inhibiting PTGS2. Polydactyly BMSC-Exos have also exhibited better capacity in promoting chondrocyte regeneration and attenuating OA in a mouse model via BMP4 signaling pathway.[236] In another animal experiment by Liu et al.,[237] MSC-Exos was administered into CIOA mice that led to an increase in chondrocyte proliferation and a decrease in chondrocyte apoptosis. Another study found that MSC-Exos reduced inflammation, restored matrix homeostasis, improved proliferation, increased matrix synthesis, and decreased apoptosis in an OA rat model of the temporomandibular joint (TMJ), therefore lowering pain and promoting TMJ regeneration.[238] Using a CIOA-induced mouse model, Mao et al.[149] found that BMSC-Exo-derived miR-92a-3p inhibited cartilage degradation and maintained homeostasis via regulating WNT5A expression. Chen et al.[239] implanted 3D-printed ECM/GelMA scaffolds with BMSC-Exos subcutaneously in rabbits with osteochondral defect. These scaffolds improved early OA treatment by rectifying cartilage mitochondrial dysfunction, increasing chondrocyte migration,

and polarizing synovial macrophages toward M2.[239] Furthermore, Wu et al.[240] demonstrated that intra-articular injections of MSC-Exos reduced cartilage damage in OA rats by inhibiting chondrocyte apoptosis, preserving cartilage homeostasis, and blocking the mTOR-autophagy pathway. Additionally, ADSC-Exos have been shown in an in vitro investigation to lessen inflammatory responses and oxidative stress in OA osteoblasts.[241] Tables 5 and 6 as well as Figure 12 display all recent publication highlighting the use of exosomes and EVs for the management of OA.[242]

3.7 | Inflammatory bowel disease

Inflammatory bowel disease (IBD) is an autoimmune disease including ulcerative colitis (UC) and Crohn's disease (CD) that significantly affects the quality of life in these patients.[158,263,264] MSC-EVs have recently been investigated in various IBD models. Heidari et al. (2021) assessed the efficacy of ADSC-Exos in a mouse model of acute colitis caused by dextran sulfate sodium (DSS).[265] In this animal model, it was demonstrated that an increase in Treg population and a decrease in inflammatory cytokines alleviated colitis.[266] Additionally, in a DSS-induced IBD animal model, intravenous injection of ADSC-Exos enhanced epithelial regeneration, decreased inflammation, and supported functional recovery while preserving intestinal barrier integrity.[266] Additionally, a recent study by Li et al.[267] found that in a mouse model of DSS-induced colitis, ADSC-Exos as well as the parent ADSCs both exhibited comparable anti-inflammatory and immunosuppressive effects. Specifically, exosomes have been shown to regulate the mechanisms involved in inflammation, hence exhibiting potential therapeutic benefits in mice with DSS-induced colitis.[268]

Exosomes have also been shown to mitigate DSS-induced IBD in mice by means of ubiquitination[269] and the control of IL-7 production in macrophages.[270] Tolomeo et al.[271] conducted a comparative investigation including MSCs and MSC-EVs. The purpose of their research was to compare the effectiveness of two different therapy strategies for treating IBD in a DSS-induced colitis mouse model.[271] The results of their study demonstrated that cytokine-primed MSC-EVs exhibited a significant reduction in intestinal fibrosis and angiogenesis, while also enhancing the functionality of the intestinal epithelium. These effects were achieved by the modulation of macrophage polarization, specifically shifting from the M1 phenotype to the M2 phenotype, as well as an increase in the number of Treg cells.[272,273] Moreover, rats exposed to 2,4,6 trinitrobenzenesulfonic acid (TNBS) developed colitis, but miR-146a-containing BMSC-EVs protected them by inhibiting IL-1 receptor-associated TNF receptor-associated factor 6 (TRAF6) and kinase 1 (IRAK1).[132] In a study by Tian et al.,[274] olfactory ecto-MSC-Exos dramatically reduced the degree of disease by downregulating Th17 and Th1 populations and upregulating Tregs in a mouse model of DSS-induced colitis. Furthermore, Duan et al.[275] investigated the possibility that EVs derived from human placental MSCs might alleviate colitis produced by TNBS in mice by inhibiting inflammation and oxidative stress. Lastly, overexpressing telomerase and hypoxia-inducible factor 1-alpha in MSCs primed with pro-inflammatory stimuli has been found to provide greater therapeutic advantages in mice with TNBS-induced colitis. According to their research, the EVs might reduce inflammation and fibrosis by producing more M2 macrophages.[276] Table 7 highlights the use of exosomes in various autoimmune diseases including IBD.

3.8 | Type 1 diabetes

In type 1 diabetes mellitus (T1DM), T lymphocytes destroy pancreatic beta cells resulting in this complicated and hard to treat autoimmune disease.[277] Environmental, immune system, and genetic variables all impact type 1 diabetes.[278,279] A study by Nakano et al.[280] assessed the efficacy of injecting rat BMSC-Exos intravenously in mice with diabetes treated with streptozotocin (STZ). In a second study utilizing the STZ-diabetic mouse model, ADSC-Exos was administered intraperitoneally to one group, whereas the other group received no treatment.[281] The autoimmune responses were significantly reduced in the treated group which led to improved regulation of IFN-γ, IL-17, IL-4, IL-10, and TGF-β. Furthermore, Shigemoto-kuroda et al. discovered that MSC-EVs could inhibit Th1 and Th17, thereby significantly increasing plasma insulin concentrations and effectively delaying the onset of T1DM in order to avoid islet inflammation.[282]

3.9 | Osteoporosis

Osteoporosis (OP) is a common complication in rheumatic diseases characterized by an imbalance between bone resorption and bone formation thereby contributing to the long-term deterioration of bone tissue including an elevated risk of bone fracture.[158,283] MiR-150-3p from BMSC-Exos was investigated by Qiu et al.[284] to reduce OP in rats. In 2020, Yang et al.[285] demonstrated that the miR-1263 produced from huc-MSC-Exos exhibited anti-apoptotic properties in osteoporosis caused by hind limb unloading (HLU) via the Mob1/Hippo axis. In a mouse model, Huc-MSC-Exos have also been shown to play a role in osteoporosis inhibition and osteogenic induction.[286] Furthermore, it was shown that ADSC-Exos relieved diabetic OP via inhibiting the NLRP3 inflammasome in rat osteoclasts.[287] A 2020 publication showed that delivering miR-22-3p generated from BMSC-EVs was a useful strategy to enhance osteogenic differentiation in mice with ovariectomized-induced OP.[288] The prevention of OP was also shown in association with cyclic mechanical stretch (CMS)-modified BMSC-Exos which function by lowering the activation of the NF-κB signaling pathway.[289] While the majority of studies to date focus on in vitro and in vivo work using exosomes for the management of osteoporosis,[290–295] there remains great interest to translate these findings toward clinical practice. Tables 7 and 8 highlights additional studies investigating exosomes on autoimmune disorders.

TABLE 5 Therapeutic application of MSCs-derived EVs-miRNAs in OA treatment.

Cells	Isolation	Agent	Loading	Quantification	Animal OA model	Biological function	References
BMSCs	UC	miR-126	Curcumin	In vitro: Not available	None	In vitro: Reverse IL-1β induced catabolic responses of chondrocytes	Li et al.[227]
SMSCs	UC	circRNA3503	Melatonin/plasmid transfection	In vitro: Not available In vivo: 100 μL sEVs (10^{11} sEV vesicles/mL) per week, 4 weeks	ACLT model with SD rats	In vitro: Rescue cells from the destructive effect of IL-1β In vivo: Protect cartilage	Tao et al.[243]
SMSCs	UC	miR-129	Mimic transfection	In vitro: Not available	None	In vitro: Reduce chondrocytes injury and ECM degradation	Qiu et al.[244]
BMSCs	UF	miR-216a	Hypoxia/lentivirus transfection	In vitro: Not available In vivo: Not available	DMM model with SD rats	In vitro: Promote chondrocytes proliferation, migration, inhibit apoptosis In vivo: Promote cartilage regeneration	Rong et al.[245]
SMSCs	UC	miR-31	Mimic transfection	In vitro: 10 mg EVs for 24 h In vivo: 5 mL EV particles per mL, from the 5th to the 8th week after operation	ACLT model with C57 mice	In vitro: Promote proliferation and migration of chondrocytes In vivo: Alleviate cartilage damage and inflammation	Wang et al.[246]
BMSCs	UF	miR-136	Agomir transfection	In vitro: Not available In vivo: 100 μL of 10^{11} particles/mL for 1 h	ACLT model with C57 mice	In vitro: Promote migration of chondrocytes In vivo: Reduce cartilage degeneration	Chen et al.[247]
BMSCs	UC	miR-124 miR-143	Curcumin	In vitro: Not available In vivo: Not available	OA model with mouse	In vitro: Reduce apoptosis of chondrocytes In vivo: Attenuate OA	Qiu et al.[248]
ADMSCs	UC	miRNAs	IFN-γ	In vitro: Not available	None	In vitro: Anti-inflammatory of inflamed chondrocytes and macrophages	Ragni et al.[249]
ADMSCs	UC	miR-145 miR-221	None	In vitro: 400 μg/mL exosomes for 48 h	None	In vitro: Promote chondrogenic regeneration	Zhao et al.[250]
UC-MSCs	UC	miR-381-3p	Kartogenin	In vitro: 20 μg/mL for 48 h In vivo: Not available	Full-thickness Cartilage defects with rabbit	In vitro: Enhance chondrogenesis In vivo: Promote cartilage repair	Jing et al.[251]
BMSCs	EQ	miR-26a-5p	Lentivirus transfection	In vitro: 2 μg exosomes for 48 h In vivo: 250 ng/5 μL EXO per week, 8 weeks	OA model with Wistar rats	In vitro/in vivo: Alleviate damage of synovial fibroblasts In vivo: Retard OA damage	Jin et al.[235]
SHEDs	UC	miR-100	Mimic transfection	In vitro: Exosomes for 2 h	None	In vitro: Anti-inflammatory in temporomandibular joint chondrocytes	Luo et al.[252]

TABLE 5 (Continued)

Cells	Isolation	Agent	Loading	Quantification	Animal OA model	Biological function	References
IMSCs	EQ/UC	miR-100	Antagomir transfection	In vitro: exosomes (1, 5, or 10×10^8 particles/mL) for 24 h In vivo: 10 μL exosomes (10^{10} particles/mL) for 4 weeks or 6 weeks (twice a week)	DMM model with rat	In vitro: Inhibit the chondrocyte apoptosis and balance the anabolic and catabolic processes In vivo: Protect cartilage and ameliorate gait patterns	Wu et al.[240]
BMSCs	EQ	miR-320c	Mimic transfection	In vitro: exosomes for 48/72 h	None	In vitro: Enhance chondrogenesis	Sun et al.[253]
MSCs	SZC	miR-135b	TGF-β1	In vitro: 10 μg/mL exosomes, 3 days In vivo: 100 μL exosomes (1×10^{11} particles/mL) per week for 12 weeks	In vivo: DMM model with rat	In vitro: Promote chondrocytes proliferation In vivo: Promote cartilage repairment	Wang et al.[254]
SMSCs	SZC	miR-140	Mimic transfection	In vitro: 10×10^{11} particles/mL of Exos for 24 h In vivo: 100 mg exosomes per 100 mL per week until 12 weeks	In vivo: DMM model with rat	In vitro: Enhance proliferation and migration of chondrocytes In vivo: Prevent OA	Tao et al.[230]

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4 | TREATMENT OF DAMAGED ORGANS

This section is dedicated to the treatment of various organs that have benefited from exosome therapy. Today, a multitude of studies have tackled the effects of exosome therapy on the treatment and aid of various organs including heart (such as myocardial infarctions and stroke), kidney, liver, and ovaries.

4.1 | Heart

Cardiovascular disease (CVD) is a significant global health issue. Based on statistics from the US Center for Disease Control and Prevention, CVDs are the primary cause of mortality in the United States.[321] Furthermore, according to an epidemiological analysis in China, the prevalence of CVD continues to rise.[322,323] As a result of societal and economic developments (especially within the aging population), the acceleration of urbanization, and changes in national living differences over the past few decades, unhealthy lifestyles are becoming increasingly common, and the effects of CVD risk factors on the health of residents are becoming more prominent/significant.

In the cardiovascular system, stem cells, vascular cells, progenitor cells, cardiomyocytes, and endothelial cells are linked and communicate with one another via exosomes. Exosomes have the ability to stimulate angiogenesis, suppress ventricular remodeling, enhance cardiac function, suppress local inflammation, and modulate immunological responses. Exosomes also have a significant impact on the growth, harm, and illness of the cardiovascular system. Nevertheless, being a relatively new field of medicine, clinical scientists are currently investigating the function of exosomes and their processes with the long-term goal of facilitating cardiac function and repair comprehensively.[324]

As a result, exosomes are crucial to the cardiovascular system and are involved in many different CVDs, including heart failure (HF), acute myocardial infarction (AMI), atherosclerosis (AS), and myocardial ischemia–reperfusion (I/R) damage as highlighted below.[324]

4.1.1 | Exosomes from different cell sources and cardiovascular signal transduction

Exosomes are effective disseminators of biological signals related to myocardial function (Table 9). In the heart, crosstalk between several cell types via EVs mediates local communication. EVs secreted by different heart cell types may also affect the same cells that release vesicles in an autocrine manner.[324] Remote communication between the heart and other organs (e.g., the kidneys, brain, and bone marrow) is mediated by EVs secreted from the myocardium entering systemic circulation. Local and distant communication comprises endocytosis, membrane fusion, or gap junction-mediated transfer, and the exchange of nucleic acids, lipids, and proteins by exosomes.[324] The mechanism by which exosomes work also includes receptor-mediated signal transduction, which regulates transcription and

TABLE 6 Therapeutic application of non-MSCs-derived EVs-miRNAs in OA treatment.

Cells	Isolation	Agent	Loading	Quantification	Animal model	Biological function	References
Chondrocytes	UC	miR-221	Mimic transfection	In vitro: 5×10^8 particles, 2 days or 2 weeks	None	In vitro: Inhibit bone formation	Shang et al.[255]
Macrophage	UC	miR-1246	Lipopolysaccharide	In vitro: 1×10^9 p/mL of sEVs for 48 h In vivo: 50 μg/μL, one time	CFA-induced TMJOA model with SD rats	In vitro: Promote inflammation In vivo: Promote TMJ inflammation	Peng et al.[256]
Fibroblast-like synoviocytes	UC	miR-126	Mimic transfection	In vitro: Not available In vivo: 40 μL of 500 μg/mL per week, until 10 weeks	ACLT + MMx OA model with SD rats	In vitro: Suppress chondrocytes inflammation and apoptosis In vivo: Maintain subchondral bone structure and suppress synovial inflammation-mediated cartilage degeneration	Zhou et al.[257]
Osteoblasts	UC	miR-210	Mimic transfection	In vitro: 20 μg/mL exosomes	None	In vitro: Promote cartilage degeneration	Wu et al.[258]
Osteoclasts	UC	let-7a	None	In vitro: Not available	None	In vitro: Promote chondrocytes hypertrophy	Dai et al.[259]
Chondrocytes	UC	miR-8485	Mimic transfection	In vitro: Not available	None	In vitro: Promote chondrogenic differentiation of BMSCs	Li et al.[260]
Chondrocytes	UC/UF	miR-449a	IL-1β	In vitro: Not available In vivo: 10^9 particles in 5 μL vehicle per week, 8 weeks	DMM OA model with mice	In vitro: Inhibition autophagy In vivo: Aggravated synovitis and cartilage erosion	Ni et al.[261]
Chondrocytes	UC	miR-95	Mimic transfection	In vitro: Not available	None	In vitro: regulate cartilage development and homeostasis	Mao et al.[262]

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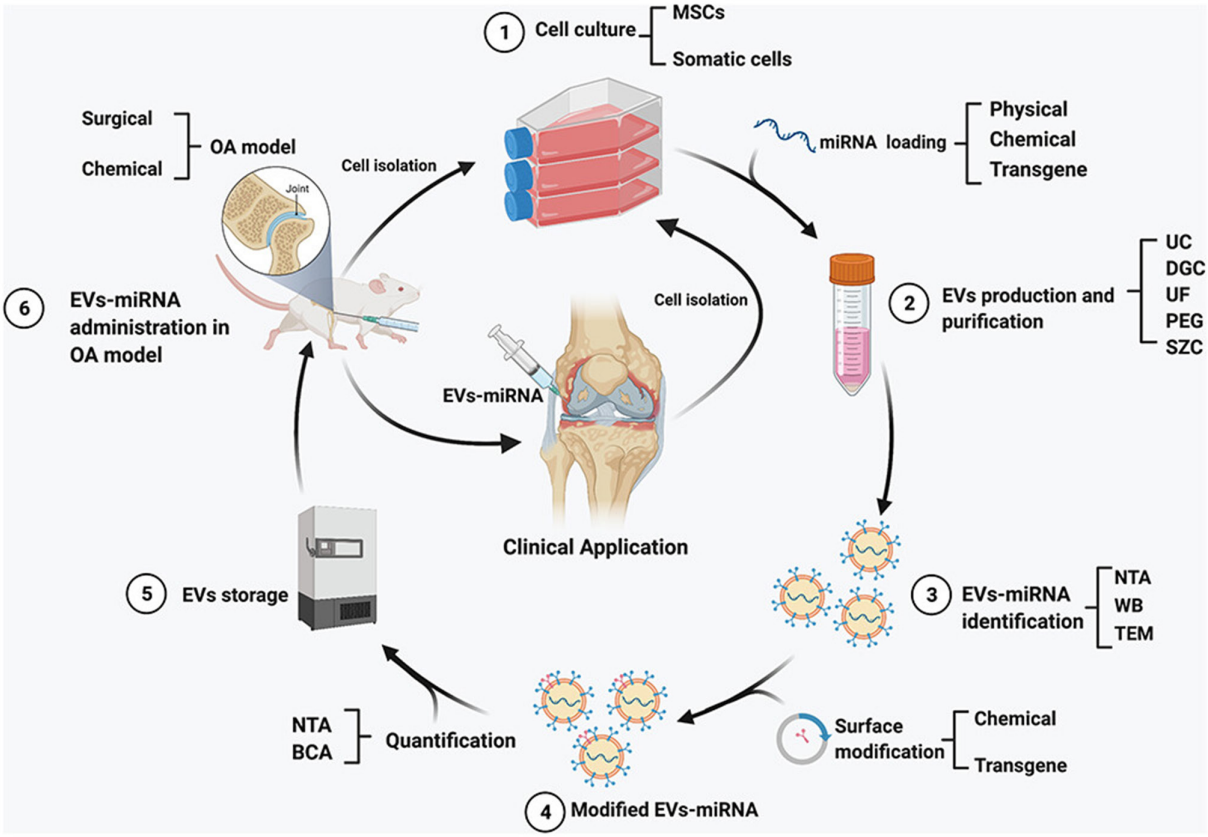

FIGURE 12 Schematic diagram of potential factors that affect the management of EVs-miRNAs, which might further affect its clinical application in human OA. Reprinted with permission from Shang et al.[242]

post-transcriptional processes in target cells. Because of these abilities, exosomes have proven to be effective disseminators of biological signals, which are involved in multiple processes that regulate cardiac function under normal physiological and pathological cardiac conditions.[324]

4.1.2 | Myocardial infarctions and injury

The restricted capacity of adult mammalian cardiomyocytes to undergo cell division in response to cardiac injuries is a significant factor toward the development of detrimental fibrotic and myocardial remodeling, eventually leading to heart failure. The persistent prevalence of heart failure-related illness and mortality necessitates the focused efforts by researchers globally to develop effective treatments for cardiac restoration.[325] Following heart damage, this lack of proliferation leads to pathological healing processes and fibrotic scarring.[326–328]

The majority of studies on stem cell therapies has demonstrated enhanced cardiac function and vascularization along with decreased infarct size despite the transplanted cells dying quickly in the damaged myocardium. This suggests that paracrine mechanisms play the most significant role in cardiac healing. It has been noted that all progenitor and stem cells used in cell-based therapies secrete substances that affect nearby cells in a paracrine manner. These exosomes are grouped around pro-angiogenic, pro-survival, proliferative, and immunogenic factors.[329–335] Noteworthy, many miRNAs have now been discovered as either being in pro-repair or pro-pathological state, as shown in Figure 13.[336]

Exosomes derived from various origins have the ability to mitigate cardiac ischemia/reperfusion (I/R) damage through the modulation of inflammation, autophagy, and apoptosis. Chen et al.[323] discovered that exosomes obtained from BMSCs containing miR-125b enhanced cell survival and decreased the rate of apoptosis by specifically targeting SIRT7. As a result, this reduces the size of myocardial infarction and inhibits harm caused by myocardial ischemia/reperfusion.[323] In another study, Zhao et al.[337] discovered that MSC-Exos employed miR-182 to alter the polarization of macrophages and suppress cardiac inflammation, therefore mitigating myocardial ischemia–reperfusion (I/R) damage in mice. Youn et al.[338–340] discovered that administering exosomes produced from cardiac progenitor cells (CPCs) directly into the animal heart may effectively inhibit cell death in acute ischemia/reperfusion damage models. Zhang and Zhang[341] discovered that serum exosomes have the potential to enhance hemodynamics and decrease apoptosis by stimulating the PI3K/AKT signaling pathway, hence reducing I/R damage. Additionally, it was observed that serum exosomes may also increase the production of inflammatory factors. The study conducted by Dai et al.[342] showed that exosomes produced from M2 macrophage exosomes mitigated myocardial I/R damage by suppressing TXNIP and deactivating the

TABLE 7 Therapeutic potential of mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) in autoimmune and rheumatic diseases.

Injury	Animal model	Infusion method	Origin of EVs	Dose of injection	Outcome	References
Inflammatory bowel disease (IBD)	Rat	Intravenous injection	BMSC-EV-derived miR-146a	100 μg	Attenuate experimental colitis by targeting TRAF6 and IRAK1	132
IBD	Mice	Intraperitoneal injection	BMSC-EVs	50 μL	Attenuate dextran sodium sulfate-induced ulcerative colitis by promoting M2 macrophage polarization	272
IBD	Mice	Intraperitoneal injection	AD-MSC-EVs	–	Have immunosuppressive and anti-inflammatory functions	267
IBD	Mice	Intravenous injection	Huc-MSC-Exo-derived miR-378a-5p	1 mg	Attenuate colitis by regulating macrophage pyroptosis via the NLRP3 pathway	296
IBD	Mice	Intravenous injection	AD-MSC-Exos	300 μg	Protect mice from DSS-Induced IBD by promoting intestinal-stem-cell and epithelial regeneration	266
IBD	Mice	Intraperitoneal injection	AD-MSC-Exos	100 μg	Alleviate acute colitis by Treg cell induction and inflammatory cytokine reduction	265
IBD	Mice	Intravenous injection	Huc-MSC-Exo-derived miR-326	1 mg	Inhibit neddylation to relieve IBD	297
IBD	Mice	Intraperitoneal injection	Huc-MSC-Exo-derived TSG-6	200 μg	Protect against IBD through restoring mucosal barrier repair and intestinal immune homeostasis	298
IBD	Mice	Intravenous injection	MSC-Exos	–	Reduce murine colonic inflammation via a macrophage-dependent mechanism	273
IBD	Mice	Intravenous injection	Olfactory ecto-MSC-Exos	60 μg	Ameliorate colitis via modulating Th1/Th17 and Treg cells	274
IBD	Mice	Intravenous injection	Huc-MSC-Exos	400 μg	Alleviate IBD through the modulation of IL-7 expression in macrophages	270
IBD	Mice	–	MSC-EVs	–	Resulted in polarization of intestinal macrophages toward and anti-inflammatory phenotype	271
IBD	Mice	–	Huc-MSC-Exos	200 μg	Possess immunosuppressive effect in vitro and exhibit a therapeutic capability in vivo through suppressing inflammation mechanism	268
IBD	Mice	–	Placental MSC-EVs	200 μg	Alleviate experimental colitis in mice by inhibiting inflammation and oxidative stress	275
IBD	Mice	Intraperitoneal injection	Human dental pulp-MSC-EVs	50 μg	Decrease fibrosis and inflammation by increasing the level of M2 macrophages	276
Type 1 diabetes mellitus (T1DM)	Mice	Intravenous injection	BMSC-Exos	0.5 μg	Improve the cognitive impairments of by repairing damaged neurons and astrocytes	280
T1DM	Mice	Intraperitoneal injection	AD-MSC-Exos	50 μg	Exert ameliorative effects through increasing Tregs, IL-4, IL-10, TGF-β and reduction in IL-17 and IFN-γ	281

TABLE 7 (Continued)

Injury	Animal model	Infusion method	Origin of EVs	Dose of injection	Outcome	References
T1DM	Mice	Intravenous injection	MSC-Exos	30 μg	Attenuate immune responses	282
Osteoarthritis (OA)	Mice	Articular injection	Synovial MSC-Exo-derived miR-155-5p	30 μL	Prevent OA via enhancing proliferation and migration, attenuating apoptosis, and modulating extracellular matrix secretion in chondrocyte	232
OA	Mice	Articular injection	BMSC-Exos	250 ng	Protect cartilage and bone from degradation in osteoarthritis	210
OA	Rat	Articular injection	BMSC-Exos	10^{10}/mL	Prevent OA by regulating synovial macrophage polarization	209
OA	Mice	Articular injection	iMSC-Exos and SM-MSC-Exos	10^{10}/mL	iMSC-Exos exerted a stronger stimulatory effect on chondrocyte migration and proliferation than did SM-MSC-Exos	229
OA	Rat	Articular injection	SMSC-Exo-derived miR-140-5p	100 μg	Enhance cartilage tissue regeneration and prevent OA of the knee	230
OA	Mice	Articular injection	Polydactyly BMSC-Exos	–	Alleviate OA by promoting chondrocyte proliferation	236
OA	Mice	Articular injection	LPS-primed SMSC-ECVs	10^{11}/mL	Inhibit ECM degradation and prevent OA	231
OA	Mice	Articular injection	Embryonic-MSC-Exos	10^{6}/mL	Alleviate OA through balancing synthesis and degradation of cartilage extracellular matrix	233
OA	Rat	Joint cavity injection	BMSC-Exos	40 μg	Promote cartilage repair and extracellular matrix synthesis, as well as alleviate knee pain	234
OA	Rat	Joint injection	Huc-MSC-Exo-derived miR-26a-5p	250 ng	Alleviate OA via downregulation of PTGS2	235
OA	Mice	–	MSC-Exo-derived KLF3- AS1	–	Elevate chondrocyte proliferation and inhibit apoptosis through miR-206/GIT1 axis	237
OA	Rat	Articular injection	Embryonic stem cell-derived MSC-Exos	100 μg	Reduce pain and repair osteoarthritic TMJs by attenuating inflammation and restoring matrix homeostasis	238
OA	Mice	–	BMSC-Exo-derived miR-92a-3p	500 μg	Enhance chondrogenesis and suppress cartilage degradation via targeting WNT5A	149
OA	Rabbit	Subcutaneous injection	ECM/GelMA/BMSC-Exos	–	Restored chondrocyte mitochondrial dysfunction, enhanced chondrocyte migration, and polarized the synovial macrophage response toward M2	239
OA	Mice	Articular injection	IPFP-MSCs-Exo-derived miR-100-5p	10^{10}/mL	Protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR	240
OA	Rat	Articular injection	AD-MSC-Exos	100 μg	Facilitate cartilage injury repair and alleviate OA	299

(Continues)

TABLE 7 (Continued)

Injury	Animal model	Infusion method	Origin of EVs	Dose of injection	Outcome	References
Osteoporosis (OP)	Rat	–	BMSC-Exo-derived miR-150-3p	–	Promote osteoblast proliferation and differentiation in osteoporosis	284
OP	Rat	Intravenous injection	GPNMB-modified BMSC-EVs	100 μg	Attenuate bone loss in an ovariectomized rat model of OP	300
OP	Mice	Intraperitoneal injection	Huc-MSC-Exos	–	Induce osteogenesis and prevent OP	286
OP	Mice	Intravenous injection	BMSC-Exos	0.1 mL	Inhibit RANKL-induced osteoclastogenesis through the NF-κB signaling pathway	289
OP	Rat	Intravenous injection	Epimedium-Preconditioned BMSC-EVs derived miR-27a-5p	100 ng	Stimulate osteogenesis by targeting Atg4B-mediated autophagy	290
OP	Rat	Intravenous injection	BMSC-Exos derived miR-186	10^{13}/mL	Promote osteogenesis through hippo signaling pathway in OP	292
OP	Rat	–	BMSC-EVs derived miR-20a	–	Promote the osteointegration of porous titanium alloy by enhancing osteogenesis via targeting BAMBI	293
OP	Rat	–	Huc-MSC-Exos derived miR-1263	–	Prevent apoptosis in disuse osteoporosis	285
Multiple sclerosis (MS)	Mice	Intravenous injection	AD-MSC-EVs	25 μg	Attenuate motor deficits through immunomodulatory actions, diminishing brain atrophy and promoting remyelination	74
MS	–	–	Huc-MSC-Exos	–	Suppress proliferation of activated PBMCs	301
MS	Mice	Intravenous injection	MSC-Exos armed with high-affinity aptamer	200 μg	Produced synergistic immunomodulatory properties and remyelination effect	302
MS	Rat	Intravenous injection	BMSC-EVs	100 and 400 μg	Attenuate inflammation and demyelination of the central nervous system in EAE rats by regulating the polarization of microglia	76
MS	Mice	Intravenous injection	Placental MSC-EVs	10^{7} or 10^{10}/mL	Promote myelin regeneration	80
Amyotrophic lateral sclerosis (ALS)	Mice	Intravenous or intraperitoneal injection	IFN-γ-primed MSC-EVs	–	Affect neuroinflammation possibly through specific immunomodulatory miRNAs acting on microglia	303
Rheumatoid arthritis (RA)	Mice	Intraperitoneal injection	BMSC-Exo-derived miRNA-150-5p	50 μg	Decrease migration and invasion and inhibiting angiogenesis in vitro and alleviating the symptoms of RA by the modulation of MMP14 and VEGF	216
RA	Rat	–	BMSC-Exo-derived miR-192-5p	50 mg	Delays inflammatory response	214
RA	–	–	BMSC-Exo-derived miR-320a	–	Regulate RA-FLSs activation by suppressing CXCL9	215

TABLE 7 (Continued)

Injury	Animal model	Infusion method	Origin of EVs	Dose of injection	Outcome	References
RA	Rat	Intravenous injection	BMSC-EV-derived miR-34a	75 μg	Reduce RA inflammation via the cyclin I/ATM/ATR/p53 axis	213
RA	Mice	Intravenous injection	BMSC-EVs	–	Exert an anti-inflammatory role on T and B lymphocytes independently of MSCs priming	208
Sjögren's syndrome (SS)	Mice	–	Labial gland-MSC-Exos	50 μg	Ameliorate SS by modulating the balance of Treg and Th17 cells	304
SS	Mice	Intravenous injection	Olfactory ecto-MSC-Exos	100 μg	Ameliorate SS by modulating the function of myeloid-derived suppressor cells	305
Systemic lupus erythematosus (SLE)	Mice	Intravenous injection	Huc-MSC-Exos	100 μg	Regulate macrophage polarization to attenuate SLE-associated diffuse alveolar hemorrhage	306
SLE	–	–	MSC-Exo-derived tsRNA-21109	–	Alleviate SLE by inhibiting macrophage M1 polarization	307
Systemic Sclerosis (SSc)	Mice	Intravenous injection	IFN-γ-Primed-MSC-EVs	250 ng	Improved lung fibrosis by modulating anti-inflammatory and antifibrotic markers	308
SSc	Mice	Intravenous injection	MSC-EV-derived miR-29a-3p	100 μg	Downregulate the expression of several pro-fibrotic, remodeling, and anti-apoptotic factors as well as methylases	309
SSc	Mice	Subcutaneous injection	MSC-Exo-derived miR-196b-5p	20 μg	Suppress skin fibrosis	310
SSc	Mice	–	BMSC-EVs	15 μg	Alleviate SSc pathogenic changes by regulating the WNT and TGF-β signaling pathways	311
SSc	Mice	–	MSC-Exos	–	Ameliorate dermal fibrosis in bleomycin-induced scleroderma	312
Chronic graft-versus-host disease (cGVHD)	Mice	Intraperitoneal injection	Huc-MSC-EVs	100 μg	Prevent skin fibrosis by suppressing the activation of macrophages and B cells immune response	313

Note: Reprinted with permission.[127]

TABLE 8 Role of MSC-Exos in the treatment of autoimmune diseases (all sources).

Disease types	Exosome source	Reactive molecules	Target cells/tissue	Mechanism of action	Effect	References
Experimental autoimmune encephalomyelitis	BMSCs	–	Microglia	Regulated the polarization of microglia	Attenuated inflammation and demyelination of the CNS	76
	HPDLSCs	–	Spinal cord	Modulated NF-KB level and inhibited NALP3 inflammasome activation	Reduced pro-inflammatory infiltration	314
	MSCs	HSP70 Galectin 1 PD-LI	Spinal cord T/B lymphocyte	Promoted the differentiation of Tregs Reduced pro-inflammatory cytokines	Reduced demyelination and decreased neuroinflammation	75
Collagen-induced arthritis	BMSCs	–	T/B lymphocyte	Regulated the differentiation of lymphocyte anti-inflammatory subtype and the release of cytokine	Decreased clinical signs of inflammation	208
	BMSCs	miR-192-5p	HFLS-RA	Upregulated RAC2	Delayed the pro-inflammatory response in RA	214
Rheumatoid arthritis	MSCs	miR-150-5p	FLS	Targeted MMP14 and VEGF to decrease migration and invasion in RA FLS	Inhibited synoviocyte hyperplasia and angiogenesis	216
	HMSCs	miR-124a	HFLS-RA	–	Inhibited the proliferation and migration of fibroblast-like synoviocyte cell line	315
Osteoarthritis	HMSCs	lncRNA-KLF3-ASI miR-206/GIT1	Chondrocytes	Promoted chondrocyte proliferation, migration, and inhibited apoptosis	Facilitated cartilage repair	138,237
Type 1 diabetes	AD-MSCs	–	T/B lymphocyte	Promoted the differentiation of Tregs and the release of cytokine	Improve islet function, and decrease blood glucose	281
	MSCs	Pdx-1	Islet	–	Induced the β cells mass regeneration	316
	ADSCs	miR-126 miR-130a miR-132 miR-let7b rniR-let7c	Penis	Promoted angiogenesis Inhibited the cavernous fibrosis	Ameliorated erectile function	317
Systemic sclerosis	MSCs	miR-151-5p	Recipient bone marrow MSCs	Inhibited IL-4Rα expression and downregulated mTOR pathway activation	Reduced the damage of recipient bone marrow mesenchymal stem cells to improve osteoporosis	318
Experimental autoimmune uveoretinitis	MSCs	–	Retina	Inhibited the chemo-attractive effects of CCL2 and CCL2 l on inflammatory cells	Reduced the infiltration of T cells subsets and other pro-inflammatory cells	319
Autoimmune hepatitis	BMSCs	miR-223-3p	Macrophages	Regulated the expression of STAT3 gene and inflammatory cytokine	Attenuated pro-inflammatory response	147
	BMSCs	miR-223	Liver	Regulated NLRP3 and caspase-1	Protected liver injury	320

Note: Reprinted with permission.[127]

TABLE 9 Exosomes from different cell sources and cardiovascular signal transduction.

Cells	Inclusions	Factor	Function
Cardiomyocytes	miR-222/143	HIF-1α, TNF-α	Induce angiogenesis
	miR-217	IL-6, CCL2/6/7	Cardiac hypertrophy, cardiac fibrosis (enhance the proliferation of fibroblasts)
Cardiac fibroblasts	miR-21-3p	Ang II	Induce cardiomyocyte hypertrophy
Cardiac endothelial cells	miR-214	16K PRL	Inhibit the senescence of endothelial cells, induce angiogenesis
	miR-146a	Erbb4, Notch1, Irak1	Reduces the metabolic activity of cardiomyocytes
	miR-143/145	KLF2	Induced atherosclerotic protective phenotype
	miR-92a-3p	THBS1 dependent mechanism	Regulating the angiogenesis
	–	ERK1/2 MAPK signaling pathway	Resistance to simulated I/R injury
	Mst1	–	Inhibiting autophagy, promoting cell apoptosis, and inhibiting glucose metabolism in cardiomyocytes
	VCAM1	–	Regulate the local inflammatory response
Smooth muscle cells	–	coagulation protein prothrombin	Regulate blood coagulation and calcification
Immune cells (dendritic cells)	–	CD4(+) T cells	Promote wound healing after MI
Immune cells (macrophages)	mir-155	–	Inhibited the proliferation of fibroblasts and enhanced inflammation.
Other heart-derived	miR-21-5p	PTEN/Akt pathway	Promotes angiogenesis and cardiomyocyte survival
Circulating exosomes	AT1Rs	Ang II	Improve blood pressure responsiveness
	miR-939-5p	iNOS-NO pathway	Promote angiogenesis
	miR-342-5p	–	Protect the heart from myocardial I/R injury
	myo-miRs	CXCR4	Systemic responses to cardiac injury

Note: Reprinted with permission from Cui et al.[324]

Abbreviations: 16K PRL, 16-kDa N-terminal prolactin fragment; Akt, Protein kinase B, also known as PKB or Rac; Ang II, Angiotensin II; AT1Rs, Ang II receptor type 1; CCL2/6/7, CC-motif chemokine ligands 2/6/7; CD4, cluster of differentiation 4; CXCR4, C-X-C motif chemokine receptor type 4; ERK1/2, extracellular signal-regulated kinase1/2; HIF-1α, hypoxia-inducible factor-1α; I/R, ischemia–reperfusion; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; KLF2, Kruppel-like factor 2; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; NO, nitric oxide; PTEN, gene of phosphate and tension homology deleted on chromosome 10; THBS1, thrombospondin 1; TNF-α, tumor necrosis factor-α; VCAM1, vascular cell adhesin 1.

TLR4/NF-κB/NLRP3 inflammasome signaling pathways. Several other studies also found positive outcomes when investigating exosomes on I/R injury.[343–345]

Zhu et al.[346] showed that exosomes produced from ADSCs enhanced the formation of new blood vessels (angiogenesis) in the ischemic hind limbs and heart of mice. This effect was mediated by the miRNA-31/FIH1/HIF-1α pathway, leading to an improvement in MI damage. Pan et al.[347] extracted exosomes from ADSCs that were either unmodified or modified with miR-146a. They then assessed the therapeutic impact of these exosomes in a rat model of acute myocardial infarction (AMI) by using hypoxia-induced H9c2 cells. The study revealed that exosomes containing miR-146a had a more pronounced effect compared with the group treated with unmodified exosomes in suppressing AMI-induced apoptosis, inflammation, and fibrosis.[347] The study further discovered that exosomal miR-146a diminishes myocardial damage caused by AMI by suppressing the EGR1-mediated TLR4/NF-κB signaling pathway.[347]

Studies in pigs of both acute and chronic MI models demonstrated that the administration of exosomes isolated from cardiosphere-derived cells improved cardiac healing by enhancing cardiac function and reducing infarct size.[348] Moreover, it was recognized that cardiac progenitor cells (CPCs) control heart repair and protection. Significantly, the exosomes obtained from CPCs also enhanced the viability and reproduction of H9C2 cells by promoting the expression of Akt and activating the Akt/mTOR pathway.[349] A pediatric investigation has shown that exosomes obtained from newborn CPCs enhanced heart function and repair. In contrast, exosomes produced from CPCs of older children need hypoxic preconditioning in order to manifest cardioprotective advantages. The observed outcomes included enhanced formation of new blood vessels (angiogenesis) and decreased formation of scar tissue (fibrosis), leading to enhanced functioning of the heart after a heart attack (infarction).[350]

In addition, exosomes produced from $CD34^+$ hematopoietic stem cells (HSCs) exhibited a significant expression of pro-angiogenic microRNAs (miRNAs), such as miR-126 and miR-130, which enhance the development of blood vessels in the damaged heart.[351] A study of miRNA sequences revealed a comparable miRNA profile between

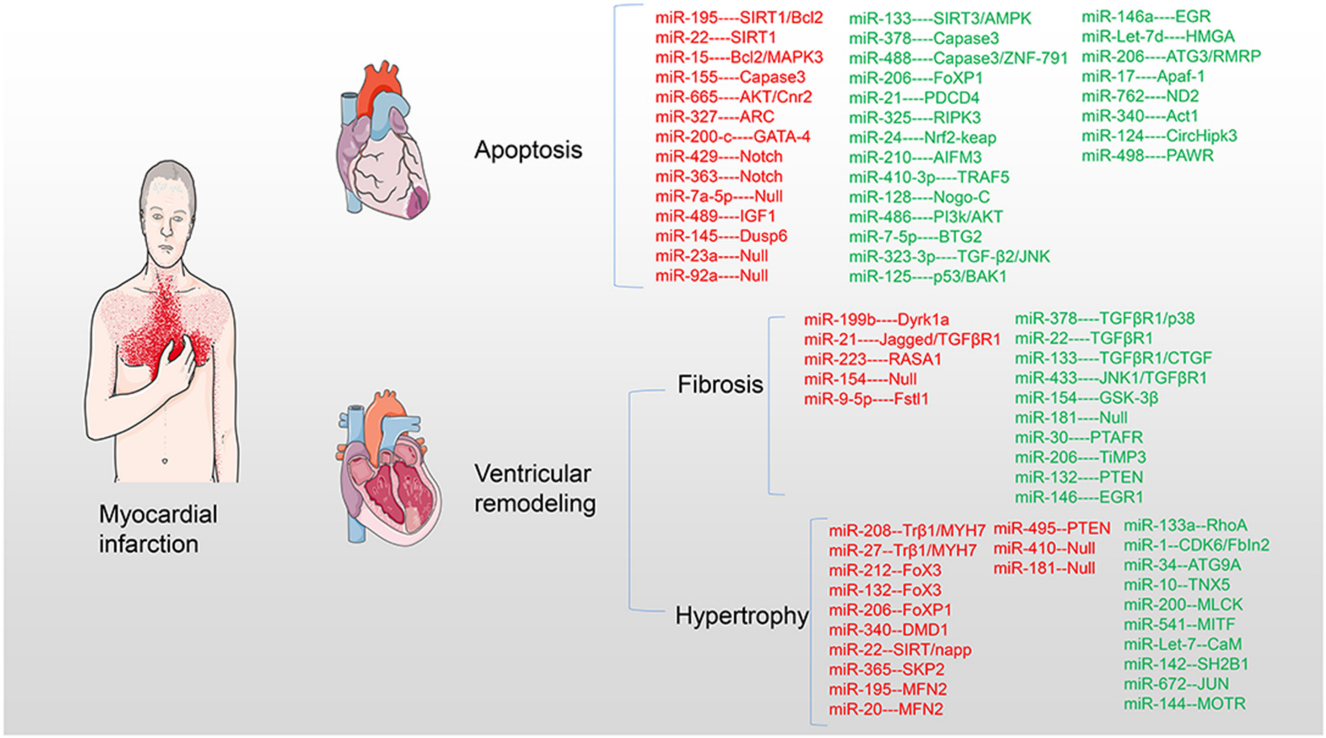

FIGURE 13 miRNAs target myocardium in pathological process after MI. miRNAs are involved in myocardial cell apoptosis, myocardial fibrosis, and myocardial hypertrophy acting on myocardial targets after MI. Upregulation of red miRNAs promoted the development of pathology, while upregulation of green miRNAs inhibited or even reversed the pathological process. Reprinted with permission from Wang and Zheng.[336]

MSCs and exosomes formed from MSCs, indicating a mechanistic commonality in the way MSCs and MSC-Exos contribute to cardiac healing. This highlights the enhanced therapeutic significance of exosomes produced from MSCs compared to MSCs themselves in the context of heart repair and has reported as being much safer.[352] Additional research has shown that exosomes obtained from MSCs that have been preconditioned under hypoxic conditions exhibit higher levels of several miRNAs associated with better cell survival, angiogenesis, and decreased fibrosis. As a result, these exosomes produced from hypoxic MSCs are more effective in promoting cardiac repair compared to exosomes derived from MSCs under normal oxygen conditions.[353–356] Additional examination shown that pre-treating CSCs with exosomes produced from MSCs also leads to enhanced viability and angiogenic capability of CSCs.[357]

4.1.3 | Hypertension

Hypertension is a prevalent global health issue that significantly contributes to the occurrence and death rates of CVDs. An estimated 1.13 billion individuals worldwide were affected by this silent illness, and the number continues to rise.[358–360] According to the American Heart Association, about 45% of individuals in the United States have uncontrolled hypertension. Vascular smooth muscle cell (VSMC) migration is crucial for the restructuring of hypertensive blood arteries, whereas adventitia fibroblasts (AFs) have a significant impact on the maintenance of vascular structures. Tong et al.[361] cultured primary VSMCs and AFs from the aorta of spontaneously hypertensive rats and Wistar-Kyoto (WKY) rats and found that AF exosomes from hypertensive rats convert Ang-converting enzyme transfer to VSMCs, thereby increasing the level of Ang II and activating the Ang II type 1 receptor (ATR) in VSMCs, thereby promoting VSMC migration.

Due to their unique properties, EVs have attracted attention as a possible prognostic and therapeutic option for the treatment of hypertension. First, EVs serve as prognostic biomarkers and may be collected using minimally invasive (circulating EVs) or noninvasive (urinary EVs) procedures. They also provide information to the clinician on the potential etiology of hypertension since EVs include components from their parent cells. It has been proposed that EVs may serve as surrogate indicators for vascular damage, endothelial dysfunction, and elevated renal sodium transporter/exchanger activity in hypertension.[362–365] Additionally, EVs may be used as indicators of enhanced vascular endothelial function.

During a 12-week course of treatment with aliskiren (a direct renin inhibitor), hypertensive patients receiving hemodialysis had increased levels of platelet-derived EVs and flow-mediated dilatation.[366] The goal of further research was to examine EVs as potential functional biomolecules as potential biomarkers.[367] These studies were employed to track the vascular health of individuals including the expression of circulating EVs and their favorable correlation with the endothelial activation marker E-selectin.[368]

Equally relevant, EVs have significant benefits as therapeutic agents. Due to their minimal immunogenicity, EV-based therapeutics have the potential to overcome many of the challenges associated with cell-based therapies.[369–371] EVs are currently in the early stages of development as a therapeutic option for hypertension. Research conducted in vivo has revealed that circulating EVs from WKY and SHRs with low plasma levels may modify the vasoreactivity of isolated mesenteric arteries in a distinct way.[372] In a preclinical model, plasma EVs had the ability to control systemic blood pressure and have a positive impact on end-organ damage caused by hypertension. While still early in the process, EV-mediated therapies for blood pressure management should be available in the near future offering much hope for the management of hypertension in a more natural way. Additionally, disease progress and resolution can be monitored by using exosomes as biomarkers throughout the disease process.

4.1.4 | Atrial fibrillation

Atrial fibrillation (AF) is the most prevalent type of cardiac arrhythmia worldwide, has a heavy socioeconomic burden, high morbidity, and death rate, as well as poses major consequences including heart failure and stroke.[373,374] It is predicted that the incidence of AF will more than double over the next 40 years, impacting 1%–1.5% of the global population. The condition's frequency is directly correlated with growing age.[375,376] An established therapy for AF, particularly for paroxysmal AF (PAF), is catheter ablation. However, since the operation is often accompanied by hazards and other clinical problems, the success rate for persistent AF (PsAF) is not optimal. Additionally, the AF lacks efficient upstream management.[377–379]

At present, there are relatively few studies on exosomes and AF, and the studies that have been conducted have mainly focused on the diagnosis of AF. Fibroblast activation of myofibroblasts is a crucial step in the pathophysiology of fibrosis. Wei et al.[380] demonstrated that the expression of miRNA extracted from the plasma of individuals with AF and normal sinus rhythm differs. Research by Mun et al.[381] established a connection between atrial shape and function, oxidative stress, and fibrosis pathways through serum exosomal miRNA and the genes it targets. Based on these findings, exosomal miRNAs show some promise as potential biomarkers for tracking AF development.

4.1.5 | Heart failure

Heart failure (HF) is a clinical state that may be caused by several disorders affecting the myocardium, cardiac valves, pericardium, or vasculature. Idiopathic dilated cardiomyopathy is one such ailment. Ischemic heart disease is another. The main symptoms of HF are usually exhaustion, edema, and dyspnea. HF is mostly caused by coronary artery disease, valve disease, hypertension, and dilated cardiomyopathy in the Western world.[382] HF is an expensive and possibly fatal illness.[383] While the lifetime risk of heart failure is already quite high (20%–45%),[384] projections indicate that the prevalence of the condition is expected to increase even further, and the spending on treatment/therapy is expected to increase by 127% by the year 2030.[385]

Chen et al.[386] discovered that exosomes obtained from BMSCs had a substantial protective effect on the myocardium against cardiac hypertrophy, reducing myocardial cell death and fibrosis, and preserving cardiac function under pressure overload conditions. Additionally, studies have demonstrated that exosomes generated from MSCs also inhibit cell hypertrophy induced by Ang II. Exosomes also stimulate the early recovery of aging of myofibroblasts in a laboratory setting, suggesting that they have beneficial effects in reducing fibrosis during cardiac remodeling. In summary, exosomes offer cardiomyocytes protection from pathological hypertrophy and hold great potential as a therapeutic option for HF.

4.1.6 | Atherosclerosis

Atherosclerosis (AS) is an inflammatory condition affecting blood vessels characterized by the buildup of lipids in the vessel walls. Accumulation results in the deposition of plaques and the narrowing of the channel's inner opening.[387,388] Smoking, obesity, diabetes, and vascular damage are significant contributors to the accumulation of fatty substances and cholesterol in the bloodstream, which is a key element in the development of the disease.[389–392] Atherosclerosis involves alterations in the characteristics of vascular systems, such as impaired function of endothelial cells (EC), increased proliferation and movement of vascular smooth muscle cells (VSMC), calcification of blood vessels, inflammation, infiltration of macrophages into the plaque, and polarization of macrophages.[393–395]

Multiple studies have shown that exosomes have a significant impact on different phases of the onset and progression of AS. They have a crucial function during inflammation, oxidative stress, and apoptosis.[396–403] Research has shown that exosomes derived from many origins may contribute to the onset and progression of AS by engaging in the NF-κB signaling pathway.[396–398] Yao et al.[396] found that the overexpression of peripheral platelet exosomal (PLT-exosomes) miR-25-3p inhibited coronary vascular endothelial cell inflammation. Further studies found that the inhibitory effect of PLT-exosomes carrying miR-25-3p is related to the NF-κB signaling pathway.[396] Zhong et al.[397] verified that exosomes obtained from fully developed dendritic cells (mDC-exosomes) have a role in endothelial inflammation and atherosclerosis (AS). The process involves the transfer of miR-146 from mDC-exosomes to HUVECs. The activation of the NF-κB signaling pathway has been shown to enhance the production of adhesion molecules in endothelial cells and shields HUVECs from further stimulation by suppressing IL-1 receptor-associated kinases. This suggests that mDC-exosomes play a key role in the feedback mechanism that regulates inflammation in a negative manner.

Oxidized low-density lipoprotein (ox-LDL) also has a significant impact on the initiation and progression of AS by activating macrophages and endothelial cells. After discovering that exosomal miR-146a, which are derived from ox-LDL-treated macrophages, Zhang et al.[400] discovered that AS in mice was greatly worsened after intravenous injection of exosomes originating from ox-LDL-treated THP-1 cells. Chen et al.[401] found that exosomal miR-505 from ox-LDL-treated vascular endothelial cells intensified AS by triggering the production of NETs.

Another study by Li et al.[399] showed that the miR-let7/HMGA2/NF-źB pathway was responsible for the improvement of AS in ApoE mice and the promotion of M2 macrophage polarization in plaques. Furthermore, exosomes produced from MSCs prevented macrophage recruitment in plaques via the miR-let7/IGF2BP1/PTEN pathway. This finding offers novel methods to reduce atherosclerotic plaque inflammation and enhances our knowledge of how MSC-Exos impact this condition. According to Lin et al.,[402] miR-203-3p was discovered to decrease cathepsin S production and AS-related characteristics in BM-derived macrophages when transferred from dendritic cell-derived exosomes (DEXs). A prospective therapeutic target for AS, the p38/MAPK signaling pathway, has emerged as a result of studies aiming to slow the progression of the disease in mice. The combined results demonstrated that exosomes mitigate the development of macrophage foam cells by modulating the expression of cholesterol transporters.[403] This discovery unveils a novel method by which PVAT safeguards the vasculature against atherosclerosis.

Figure 14 summarizes the number of findings derived from extensive studies on exosomes as therapeutic agents for the treatment of various heart conditions. These studies have shown that exosomes promote angiogenesis, encourage the polarization of M2 macrophages, reduce the presence of pro-inflammatory immune cells, and mitigate the antifibrotic properties of the injury.[404]

4.2 | Stroke

Ischemic strokes are a major contributor to chronic disability worldwide, and there are few therapies that are successful. Mounting data indicate that exosomes have a role in ischemic disease and have beneficial therapeutic benefits by facilitating cell-to-cell contact in individuals with significant impairment and substantial economic constraints.[405,406]

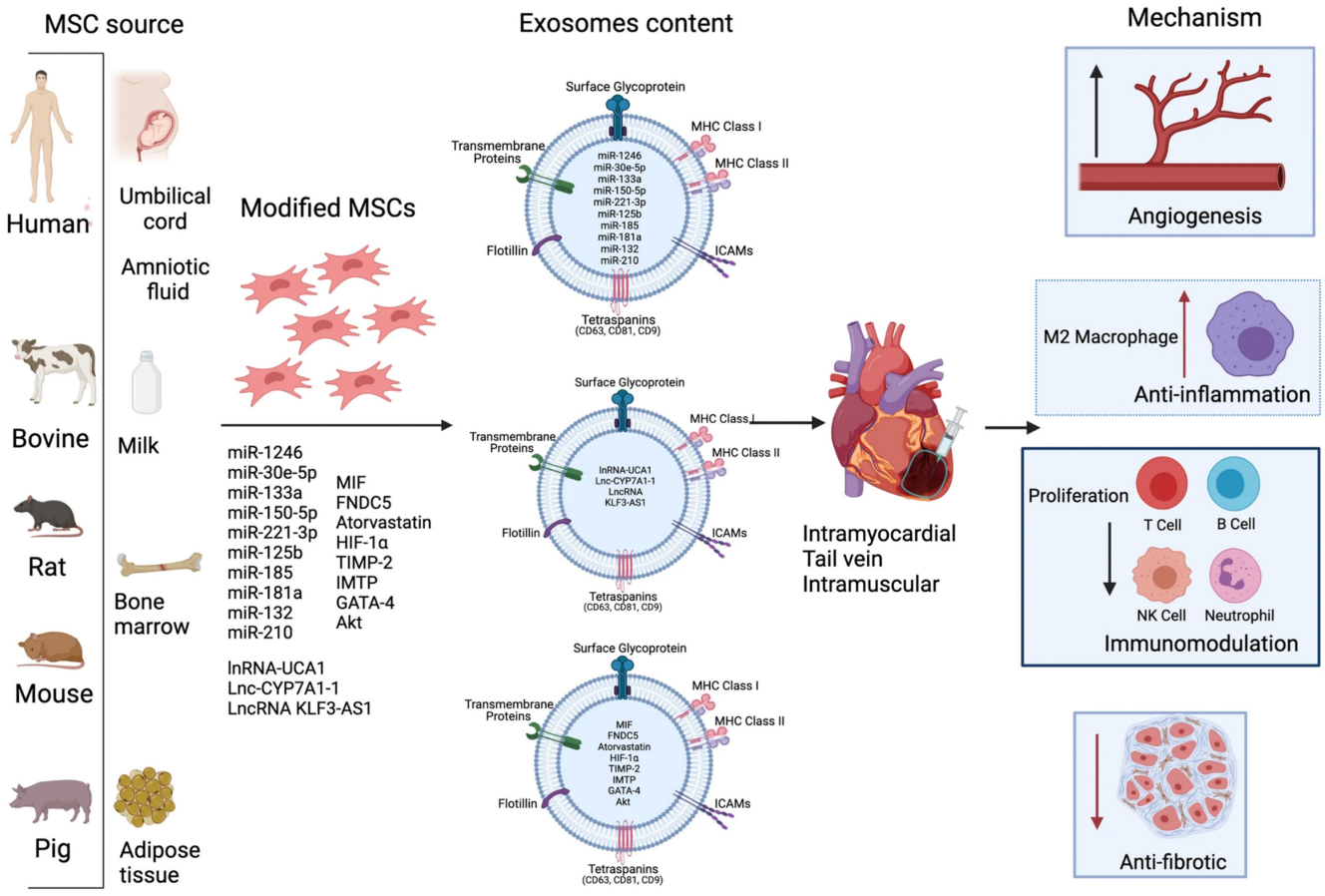

FIGURE 14 Mesenchymal stromal cell (MSC)-derived exosomes for cardiac repair and function. Exosomes isolated from different sources of MSCs carry and deliver proteins, nucleic acids (DNA, miRNAs, mRNAs, and other RNAs), and metabolites to the damage heart tissue, consequently promoting cardioprotective effects. Reprinted with permission from Joladarashi and Kishore.[404]

The inflammatory response may be seen as both beneficial and detrimental in the progression of cerebral ischemia.[407–409] The narrow treatment window (<4.5 h) and methodological limitations of ischemic strokes have led to a focus on innovative techniques in clinical research. Inflammation may cause the immune system to become overactive in the early stages of a stroke as inflammatory factors or biological components produced by dying cells stimulates resident microglia and invades peripheral immune cells. Following this, these cells release a range of inflammatory mediators, chemokines, adhesion molecules, tissue-degrading enzymes, and complement system activators.[410–412] Together, they worsen brain injury and accelerate BBB degradation in a vicious cycle.[411]

4.2.1 | MSC exosomes for stroke therapy

Clinical investigations and animal models have shown that MSC transplantation may facilitate recovery after a stroke (Table 10).[413] Increasing data supports the concept that that stem cells primarily exercise their therapeutic benefits via paracrine processes, with a particular focus on the release of exosomes.[414,415] MSC-derived exosomes have been shown to effectively enhance stroke recovery in cases of ischemia.

Findings have most commonly utilized intravenous delivery of exosomes. It was demonstrated in a rat model that intravenous delivery of MSC exosomes improved function and recovery in the transient middle cerebral artery occlusion (tMCAO) paradigm by stimulating neurogenesis, neurite remodeling, and angiogenesis.[417] The results demonstrated that MSC exosomes and MSCs themselves had almost identical effects on neuroprotection, angiogenesis, and immunomodulation.[418,419] Exosomes produced from brain extract-treated or oxygen–glucose deprivation (OGD)-treated MSCs also demonstrated superior therapeutic benefits. This may be based on the fact that their exosomes were enriched with certain functional proteins.[420,426]

Interestingly, MSC-Exos were also shown to be beneficial in a stroke model in primates. The recovery of fine hand motor function was aided by intravenous injection of MSC-Exos 24 h and 14 days after the damage in the macaca mulatta cortical hand motor brain injury model.[432] Additional mechanistic research revealed that in old macaca mulatta, MSC-Exos not only decreased neuroinflammation but also changed the roles of microglia into restorative ones.[430] Furthermore, it impeded hyperexcitability caused by damage and reinstated the equilibrium between excitatory and inhibitory processes.[431] These effects may be explained by the transfer of functional miRNAs or proteins and the subsequent activation of downstream signaling pathways. Prior to ischemia, intranasal administration of MSC-Exos decreased neuronal mortality, encouraged the formation of oligodendroglia, and suppressed microglia-mediated neuroinflammation, perhaps via the Toll-like receptor 4/CD14/NF-kB signaling pathway.[427,433]

MSC-Exos further improved the hippocampus spatial learning and memory impairments in global ischemia, perhaps via cyclo-oxygenase-2 expression regulation.[425] MSC-Exos facilitated axonal sprouting and encouraged the restoration of white matter in cases of subcortical ischemia.[424] In vitro, the enhancement of axonal development was facilitated by the transfer of miR-17-92 cluster via exosomes, which then activated the PTEN/mTOR signal pathway.[434] Exosomal miR-134 targeted caspase-8 to prevent oligodendrocytes from undergoing apoptosis.[435] Another research group that utilized lentiviruses in both knockdowns and knock in miR-133b in MSCs revealed that exosomal transfer of miR-133b to astrocytes and neurons was a partial mechanism by which MSCs mediated their effects.[436] MSC-Exos prevented neurons in OGD from dying by transferring let-7-5 p and then suppressing the production of caspase-3.[437]

Lately, there has been a growing interest in developing techniques to optimize the therapeutic potential of exosomes using engineering methodologies (Figure 15).[438,439] For example, MSC-Exos that were enhanced with the miR-17-92 cluster showed more significant enhancements in oligodendrogenesis, neurogenesis, and neurite remodeling when compared to the control group.[144] Researchers in a mouse photothrombosis model enhanced the properties of MSC-Exos by including rabies virus glycoprotein (RVG), a peptide that targets neurons. This was achieved by fusing RVG with exosomal protein lysosome-associated membrane glycoprotein 2b (Lamp2b). Subsequently, the exosomes were loaded with miR-124-mimics using electroporation. The engineered exosomes demonstrated effective transportation of miRNA-124 to the area affected by ischemia, resulting in the improvement of brain injury through facilitation of neural progenitor differentiation.[423]

4.2.2 | Neural stem cell-derived exosomes for stroke therapy

Since 2018, there has been major interest in studies on exosomes produced from neural stem cells (NSCs) in stroke patients (Table 11). In a thromboembolic stroke model, the effects of exosomes from NSCs and MSCs—both of which were derived from the same pluripotent stem cell line—were compared. It was found that NSC exosomes improved the function and reduced infarct volume more than MSC-Exos, which were linked to a more potent effect in polarizing macrophages toward an M2 phenotype and reducing inflammation.[441] Furthermore, the maintenance of astrocyte activity may be a contributing factor to the efficacy of NSC exosomes in lowering infarct volume.[442] In a senior stroke rat model, NSC exosomes showed encouraging therapeutic benefits.[441] Significantly, NSC exosome therapy improved white matter integrity and function recovery in a porcine stroke model while also reducing infarct volume and brain edema.[443]

4.2.3 | Adipose-derived stem cells derived exosomes for stroke therapy

Adipose-derived stem cells (ADSCs) have also shown promise as an ischemic therapy option and are readily acquired from surgically

TABLE 10 Published studies of mesenchymal stem cell-derived exosomes in ischemic stroke.

Animals	Stroke model	Time of treatment	Routes of exosome delivery	Exosome modifications	Proposed mechanisms	References
Rat	2 h tMCAO	24 h after ischemia	Tail vein	No	Promote neurite remodeling, neurogenesis, and angiogenesis	417
Mouse	30 min tMCAO	1, 3 and 5 days after ischemia	Femoral vein	No	Immunomodulation	418
Rat	30 min tMCAO	1, 3 and 5 days after ischemia	Femoral vein	No	Immunomodulation	419
Rat	pMCAO	48 h after ischemia	Common carotid artery	No	Promote angiogenesis, neurogenesis, anti-inflammation	420
Ovine fetuses	25 min global hypoxia-ischemia	1 h and 4 days after ischemia	Intravenously	No	Preserve baroreceptor reflex sensitivity and reduce white matter injury	421
Rat	2 h tMCAO	24 h after ischemia	Intravenously	Enriched in miR-17-92 cluster	Enhance oligodendrogenesis, neurogenesis, and neurite remodeling	144
Mouse	30 min tMCAO	Once every other day for 14 days after ischemia	Tail vein	RGD-exosomes loaded with miR-210	Promote VEGF expression and angiogenesis	422
Mous	Photothrombosis	24 h after ischemia	Tail vein	RVG-exosomes loaded with miR-124	Promote neurogenesis	423
Rat	Endothelin-1 subcortical stroke	24 h after ischemia	Tail vein	No	Promote white matter repair	424
Mouse	5 min bilateral common carotid arteries occlusion	Right before ischemia	Intracerebroventricular injection	No	Inhibition of Cox-2 expression	425
Rat	2 h tMCAO	Immediately after ischemia	Tail vein	No	Reduce oedema	426
Rat	Perinatal brain injury	Before ischemia	Intranasally	No	Neuroprotection, anti-inflammation	427
Rat	2 h tMCAO	24 h after ischemia	Intra-arterially	Enriched with miR-134b	Promote neurite remodeling	428
Macaca mulatta	Cortical hand cerebral injury	24 h and 14 days post-injury	Intravenously	No	Not studied	429
Aged macaca mulatta	Cortical hand cerebral injury	24 h and 14 days post-injury	Intravenously	No	Reduce inflammation, shift microglia toward restorative functions	430
Macaca mulatta	Cortical hand cerebral injury	24 h and 14 days post-injury	Intravenously	No	Dampen injury-related hyperexcitability restores excitatory–inhibitory balance	431

Note: Modified with permission Li et al.[416]

Abbreviations: RVG, rabies virus glycoprotein; tMCAO, transient middle cerebral artery occlusion; VEGF, vascular endothelial growth factor.

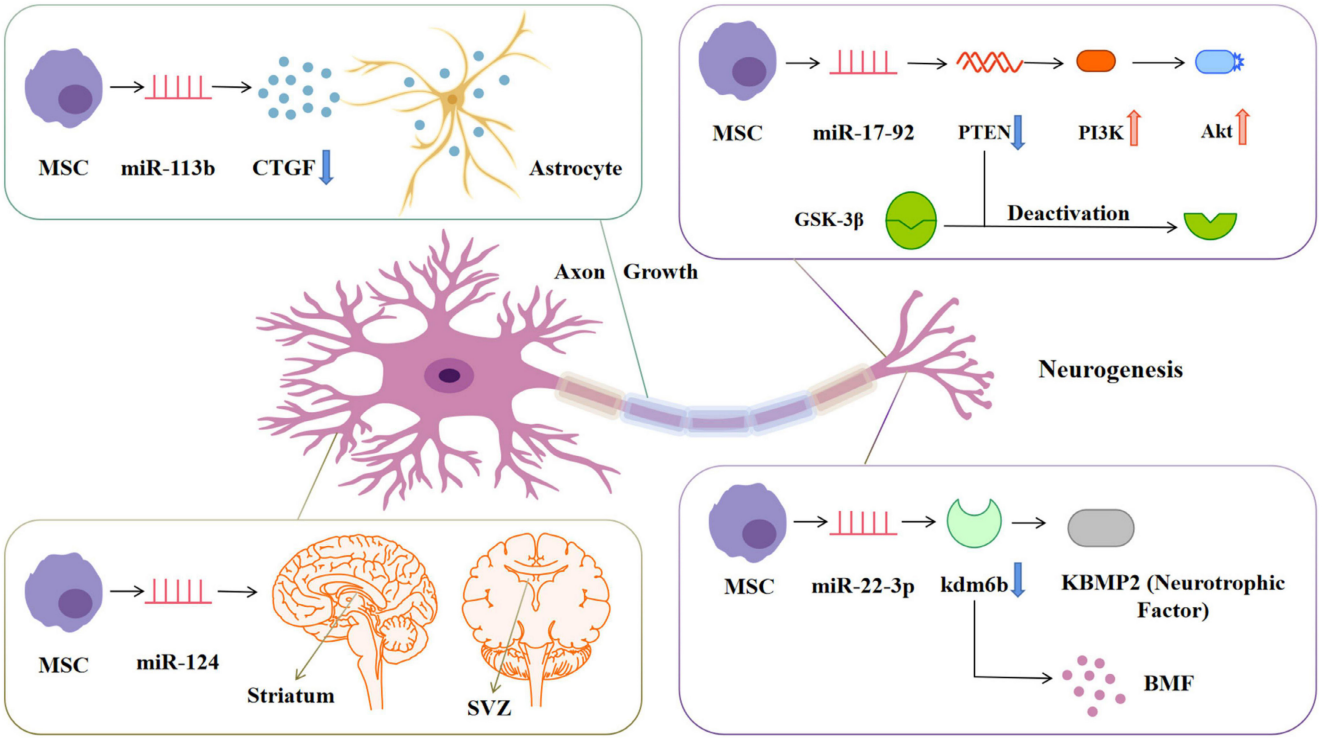

FIGURE 15 MiRNAs in exosomes secreted by mesenchymal stem cells stimulate cell and structure growth. miRNA-133b can downregulate the expression of CTGF in astrocytes, reduce the formation of glial scar, and promote the remodeling of myelin sheath. miRNA-17-92 can downregulate the expression of PTEN, thereby activating the PIK3-Akt pathway and inactivating GSK-3b, promoting the growth of neuronal axons. miRNA-124 promotes neurogenesis in SVZ and striatum regions. miRNA-22-3p can inhibit KDM6B-mediated KBMP2/BMP pathway and play a neurotrophic role. Akt, protein kinase B; BMP, bone morphogenetic protein; CTGF, connective tissue growth factor; GSK-3b, glycogen synthase kinase-3b; KBMP2, neurotrophic factor; KDM6B, lysine(K)-specific demethylase 6B; PIK3, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; SVZ, subventricular zone. Reprinted with permission from Xiong et al.[440]

removed adipose waste tissue. Exosomes from ADSCs are becoming increasingly popular as a replacement treatment (Table 12).[444] While miR-181b-5p was customized, ADSC exosomes enhanced brain micro-vessel endothelial cell migration and tube formation in vitro.[445] In rats with ischemic conditions, systemic injection of ADSC exosomes overexpressing miRNA-126 has the potential to efficiently suppress neuroinflammation, decrease neuronal death, stimulate neurogenesis, and aid in functional recovery when compared to normal and miRNA-126 knockdown ADSC exosomes.[446] ADSC-Exos enriched in miR-30d-5p protected brain damage like the normal and knockdown groups via enhancing M2 microglia polarization. A mechanistic investigation on beclin-1 and autophagy-related genes found that MiR-30d-5p inhibited M1 microglia polarization.[447] Intraventricular injection of ADSC exosomes modified with a multifunctional protein pigment epithelium-derived factor inhibited neuronal death by upregulating the expression of autophagy-associated proteins in a rat ischemia model.[448]

4.2.4 | Other cell-derived exosomes for stroke therapy

Other cell-derived exosomes, including microglia, endothelial cells, and astrocytes, have shown therapeutic benefits in stroke patients (Table 13). Exosomes generated from astrocytes have been shown to control autophagy, decrease infarct volume, and prevent neuron death.[450] By releasing miR-92b-3p, exosomes from OGD-preconditioned astrocytes reduced OGD-induced neuronal death.[451] Sema-3A inhibitors may decrease astrocyte activation and increase axonal elongation in rats with persistent ischemia via activating the GTPase-1/R-Ras/Akt/GSK-3β signaling pathway. Additionally, the authors confirmed that exosomes from astrocytes treated with OGD Sema-3A inhibitors enhanced neuron axonal outgrowth more than exosomes from both normal and OGD astrocytes.[452]

Exosomes derived from normal microvascular endothelial cells were shown to prevent astrocyte death in vitro, lessened BBB disruption, decreased infarct volume, and aided in the restoration of neurological function in vivo.[453] In contrast, exosomes from OGD endothelial cells had the opposite effects.[453] These inconsistencies may be explained by variations in the exosomal protein and miRNA contents that were separated from the same cells under differing cell culture conditions.[457]

To improve cell migration and invasion during OGD, SH-SY5Y cells were exposed to exosomes produced by OGD human umbilical vein endothelial cells (HUVEC) resulting in cell death reduction.[458] Furthermore, exosomes from endothelial cells inhibited the activation of macrophages and inflammation by transferring miR-10a and blocking the NF-kB signaling pathway.[459]

TABLE 11 Published studies of neural stem cell-derived exosomes in ischemic stroke.

Animals	Stroke model	Time of treatment	Routes of exosome delivery	Exosome modifications	Proposed mechanisms	References
Mouse	TE-MCAO	2, 14, 38/6, 24, 48 h (in aged mice) after ischemia	Tail vein	No	Immunomodulation, inhibit inflammation	441
Mouse	1-h tMCAO	2 h after ischemia	Internal jugular vein	No	Preserve astrocyte function	442
Pig	pMCAO	2, 14, 24 h after ischemia	Intravenously	No	Protect the integrity of BBB and WM	443

Note: Modified with permission Li et al.[416]

Abbreviations: BBB, blood–brain barrier; pMCAO, permanent middle cerebral artery occlusion; TE-MCAO, thromboembolic middle cerebral artery occlusion; WM, white matter.

TABLE 12 Published studies of adipose-derived stem cell-derived exosome in ischemic stroke.

Animals	Stroke model	Time of treatment	Routes of exosome delivery	Exosome modifications	Proposed mechanisms	References
Rat	50-min tMCAO	3 h after ischemia	Intravenously	No	Anti-inflammation, anti-apoptosis	449
Rat	tMCAO	Immediately after ischemia	Tail vein	Enriched with miR-30d-5p	Reduce autophagy and inflammation, and promote microglia M2 polarization	447
Rat	tMCAO	Not mentioned	Intravenously	Enriched with miR-126	Promote neurogenesis, angiogenesis, anti-inflammation	446
Rat	1-h tMCAO	3 days before ischemia	Lateral cerebral ventricle injection	Loaded with pigment epithelium-derived factor	Promote autophagy	448

Note: Modified with permission Li et al.[416]

Abbreviation: tMCAO, transient middle cerebral artery occlusion.

Interestingly, a research model using diabetic mice were given brain endothelial cell exosomes intravenously 3 days after ischemia was induced. Their neurological and cognitive results improved, and the findings demonstrated an increased myelin density and axon outgrowth, stimulated angiogenesis, and more M2 macrophage polarization.[454] These positive benefits were significantly diminished when endothelial cell exosomes with reduced levels of miR-126 were utilized.[454]

Lastly, exosomes derived from BV2 microglia cells that were activated with IL-4 enhanced the process of HUVEC tube formation.[460] Systemic delivery of M2 microglial exosomes decreased the size of the infarct, encouraged the restoration of neurological function, and prevented the death of neurons, potentially via transferring miR-124 and modifying ubiquitin-specific protease 14 in neurons.[456] The culmination of these findings suggest the importance of exosomes in intercellular communication and their potential therapeutic use for stroke management (Table 14).

4.2.5 | Routes of exosome administration for stroke therapy

Exosome administration pathways in stroke may be categorized into two main groups: systemic and local administration. Subcutaneous, intraperitoneal, intranasal, and intravenous injections into the tail vein, femoral vein, or internal jugular vein are all examples of systemic administration methods. The majority of exosomes administered to rats with ischemic stroke models enter the bloodstream via the tail vein.[417,423,424,441,447,453,456] When indium-111-labeled exosomes were administered 1 h after ischemia, single photon emission CT (SPECT) imaging revealed that the exosomes first arrived at the infarcted region and were mostly removed from the brain by the next day.[441] A further investigation showed that the process of exosomes being eliminated from the bloodstream started promptly after 1 h and continued progressively for a duration ranging from 1.5 to 6 h after injection.[476]

Using a rat model of prenatal brain damage, a thorough investigation of intranasally administered exosomes before the occurrence of ischemia showed that exosomes were seen in the frontal cortex as soon as 30 min after administration and were equally distributed throughout the whole brain 3 h after being administered.[427] The analysis of biodistribution after cerebral ischemia demonstrate that the quantity of exosomes supplied intranasally and labeled with gold nanoparticles was more than twice as high in the brain compared to those administered intravenously. Following intranasal distribution, a significant quantity of exosomes remained in the brain, while there was an almost minimal amount following intravenous delivery 24 h

TABLE 13 Published studies of other cell-derived exosomes in ischemic stroke.

Animals	Stroke model	Time of treatment	Source of exosomes	Routes of exosome delivery	Exosome modifications	Proposed mechanisms	References
Mouse	pMCAO	1 h after ischemia	Astrocyte	Tail vein	No	Anti-apoptosis	450
Mouse	90 min tMCAO	30 min after ischemia	Brain microvascular ECs	Tail vein	No	Protect BBB integrity, inhibit astrocyte activation	453
Mouse	Photothrombosis	3 days after ischemia	Brain endothelial cells	Intravenously	Enriched with miR-126	Promote angiogenesis, neurogenesis and M2 macrophage polarization	454
Rat	2 h tMCAO	Immediately after ischemia	Macrophage cell line	Tail vein	No	Promote M2 microglial polarization	455
Mouse	90 min tMCAO	1, 2, 3 days after ischemia	Microglia cell line	Tail vein	No	Promote neuronal survival	456

Note: Modified with permission Li et al.[416]

Abbreviations: pMCAO, permanent middle cerebral artery occlusion; tMCAO, transient middle cerebral artery occlusion.

after injection. Significantly, a considerable proportion of exosomes supplied by the nasal route also gathered in the lungs, spleen, and kidney.[477] The findings indicated that delivering exosomes via the nose was a more effective and promising noninvasive treatment approach for ischemic stroke.

The typical method of administering local anesthesia involves injecting it into the brain ventricle.[425,448] Intracerebroventricular injection of MSC-Exos prevented cyclo-oxygenase-2 expression, enhanced spatial learning and memory, and restored hippocampal synaptic transmission impairments in global ischemia.[425] Furthermore, infarct volume and cell apoptosis were improved 3 days after tMCAO by ADSC exosomes administered via the lateral cerebral ventricle for approximately 3 days before ischaemia.[448]

4.2.6 | Exosome clinical trials in stroke

Exosomes were shown in clinical pilot studies to be adequate in promoting neurovascular remodeling and functional recovery after ischemic stroke. To encourage the translation of exosomes into the clinic, well-designed clinical trials are necessary since the clinical studies of exosome-based treatment for stroke have just recently started. To date, documented clinical studies (NCT03384433) are presently being investigated in patients on the use of exosomes to treat stroke with IRB approval. Clinical investigators are still debating the best route of MSC-Exo administration. Patients in this clinical study received 200 mg of MSC exosomes 1 month following the commencement of ischemia. 12 months after the delivery of exosomes, the modified ranking scale and adverse treatment-related events were measured.

Remarkably, the majority of clinical studies concentrate on the functions that miRNAs play in stroke in terms of prognosis, diagnosis, and prediction. For instance, the analysis of blood miRNAs from 1523 controls aged 40–69 years and 173 cases of cerebrovascular illness aged above 69 years is being investigated to determine serum miRNAs for the prediction of stroke risk. They discovered 10 miRNAs that connected with a projected risk of stroke (miR-1268b, miR-4433b-3p, and miR-6803-5p).[478] The purpose of clinical trials NCT04175691 and NCT04230785 is to use next-generation sequencing to examine patients' expression patterns of circular RNA, microRNAs, and long non-coding RNA. The trials will then investigate and differentiate related biomarkers that can be utilized to detect and predict the outcome of acute ischemic stroke, as well as track the progression and prognosis of acute ischemic stroke patients undergoing endovascular treatment. A final clinical study (NCT03577093) aims to explore the molecular pathways via which microRNA-494 regulates the cell cycle after cerebral ischemia. These investigators intend to collect peripheral blood DNA samples from individuals aged 18–80 who had a stroke within 6 h. Over the coming years, additional exosomal signals and pathways will be discovered including their ability to aid in neuroprotection (Figure 16).

4.3 | Liver

A number of articles have now been published on the use of exosomes for the management or treatment of various illnesses/diseases involving the liver. These include acute liver failure, drug-induced liver injury, hepatocellular carcinoma, and viral and alcohol-induced hepatitis and cirrhosis.

TABLE 14 Therapeutic effects of exosome on stroke by targeting microglia polarization.

Exosome	Objectives	Contents	Significance	Mechanism	References
Exosomes from serum of young rats	Aged ischemic rats	More CD46, less C1q, C3a, C3b	Improved short and long-term functional outcomes after ischemic stroke and reduced synaptic loss	Reducing $Iba1^+$ $CD86^+$ microglia but increasing $Iba1^+$ $CD206^+$ microglia	462
EVs from serum	AIS patients	hsa-miR-124-3p	Reduced serum pro-inflammatory cytokines and the NIHSS score	Reversing the LPS-induced inflammatory effect in BV2 microglia by inhibiting the expression of GRB2 and AKT3 gene involved in pro-inflammatory signaling pathways	463
Exosome from ADSCs	AIS rats	miR-30d-5p	Reduced cerebral injury	Suppressing autophagy and promoting M2 microglia polarization	460
Exosomes from serum	Endotoxemia mice	miR-15a, miR-15b, miR-21, miR-27b, miR-125a, miR-146a, and miR-155	Increased systemic pro-inflammatory cytokine production, and elevated CNS expression of pro-inflammatory cytokine mRNA and the inflammation-associated miR-155	Inducing the expression of Iba-1 and microglial uptake of exosomes derived from serum-containing inflammation-related miRNAs	464
Exosomes from BMSCs	ICH rats	miR-146a-5p	Improved neurological function and reduced neuronal apoptosis	Inhibiting microglial M1 polarization by downregulating the expression of IRAK1 and NFAT5	465
Exosomes from hUMSCs	Ischemic mice	miR-146a-5p	Improved recovery of function, attenuated microglia-mediated inflammation	Decreasing $IBA\text{-}1^+$ $CD16^+$ cells and increasing $IBA\text{-}1^+$ $CD206^+$ cells by suppressing IRAK1/TRAF6 signaling pathway	466
EVs from neural progenitor cell	MCAO mice	let-7g-5p, miR-99a-5p, let-7i-5p, miR-139-5p, miR-98-5p, miR-21-5p, and let-7b-5p	Suppressed inflammation response	Inhibiting the expression of Iba-1 and MAPK of an inflammation-related pathway	467
Exosome from BMSCs	MCAO rats	NR	Attenuated cerebral ischemia–reperfusion injury-induced neuroinflammation and pyroptosis	Shifting M1-polarized microglia shifted toward M2-polarized microglia	468
Exosomes from macrophage	pMCAO rats	Edaravone	Enhanced neuroprotection	Promoting the polarization of microglia from M1 to M2	469
Exosomes from plasma	pMCAO rats	Melatonin	Decreased infarct volume, improved recovery of function, and reduced microglia pyroptosis	Inhibiting TLR4/NF-κB pathway-mediated microglial inflammation and NLRP3-mediated microglia pyroptosis	470
Exosomes from hUMSCs	tMCAO rats	CCR2	Enhanced oligodendrogenesis and remyelination	Decreasing CD16 and IL-1β mRNA expression and increasing CD206 and Arg-1 mRNA expression	471
Exosomes from LPS stimulated macrophage	MCAO/R rats	NR	Increased neuroprotection and functional improvement	Enhancing the microglial polarization from M1 phenotype to M2 phenotype	472
Exosomes from ADSCs	MCAO/R rats	miR-126	Improved neurogenesis and functional recovery	Inhibited microglial activation and the expression of inflammatory factors	473

TABLE 14 (Continued)

Exosome	Objectives	Contents	Significance	Mechanism	References
Exosomes from MSCs	MCAO/R rats	miR-223-3p	Decreased cerebral infarct volume, improved neurological deficits, learning and memorizing abilities	Inhibiting microglial M1 polarization mediated pro-inflammatory response	474
Exosomes from human embryonic kidney cells	Photothrombotic ischemic mice	NGF and NGF mRNA	Reduced ischemic injury via reducing inflammation and cell death	Reducing $CD16^+$ M1 microglia but increasing $CD206^+$ M2 microglia	475

Note: Reprinted with permission from Wan et al.[461]

Abbreviations: ADSCs, adipose-derived stem cells; AIS, acute ischemic stroke; BMSCs, bone marrow mesenchymal stem cells; C1q, complement component 1q; CCR2, C-C chemokine receptor type 2; CNS, central nervous system; CysLT2R, cysteinyl leukotriene receptor 2; EVs, extracellular vesicles; HUC-MSCs, human umbilical cord mesenchymal stem cells; ICH, intracerebral hemorrhage; IRAK1, interleukin 1 receptor-associated kinase 1; LPS, lipopolysaccharide; MCAO/R, middle cerebral artery occlusion and reperfusion; MSCs, mesenchymal stem cells; NFAT5, nuclear factor of activated T cells 5; NF-κB, nuclear factor-κB; NGF, nerve growth factor; NIHSS, National Institutes of Health Stroke Scale; NLRP3, NLR family pyrin domain-containing 3; NR, not reported; OGD, oxygen–glucose deprivation; pMCAO, permanent middle cerebral artery occlusion; STAT3, signal transducer and activator of Transcription 3; TLR, toll-like receptor; tMCAO, transient middle cerebral artery occlusion; TRAF6, TNF receptor-associated factor 6; USP14, ubiquitin-specific protease 14.

4.3.1 | Acute liver failure

Acute liver failure (ALF) manifests 24 weeks after the beginning of the first symptoms[480] and are categorized depending on the time and intensity of their clinical presentation: hyperacute, acute, and subacute.[481] Fulminant hepatic failure is present in both the hyperacute and acute forms, although subacute variants are also known as subfulminant.[482] Remarkably, the fatality rate is lower among individuals who develop hepatic encephalopathy 8 weeks after the first symptoms (fulminant hepatic failure) when compared to those with a more progressive progression.[483] Multiorgan failure (MOF) is the primary reason (>50%) for death in cases of ALF, with intracranial hypertension (ICH) and infection being the other significant causes of mortality in this group of patients.[484]

Shokravi and colleagues conducted a thorough review paper examining the use of stem cells and their exosomes in the context of acute liver failure (ALF).[485] It has been shown that the usage of MSCs affects how cells differentiate into hepatocytes, reduce inflammation, possess antifibrotic effects, and help release and absorb antioxidants.[485] Exosomes have been shown to be much safer with their effects examined in Table 15. In summary, exosomes have been shown to reduce oxidative stress, enhance angiogenesis, enhance liver survival and function, and lessen inflammation in the liver overall.

4.3.2 | Drug-induced liver injury

Drug-induced liver injury (DILI) is a prominent factor in cases of acute liver injury (ALI), leading to black box warnings and the removal of medications from the market. This condition may be attributed to over 1000 pharmaceuticals that are presently accessible.[499–501] Nonsteroidal anti-inflammatory, anti-infectious, psychotropic, and hypolipidemic medications were the most frequently implicated pharmaceuticals.[502,503]

Recent findings indicate that exosomes in circulation and their contents may serve as noninvasive sources of prospective molecular biomarkers for their early identification, tracking, and assessment of DILI. Additionally, it was shown that exosomes present in urine contained RNAs or proteins suggestive of DILI. Exosomes derived from hepatocytes or mesenchymal stem cells are also thought to be promising therapeutic agents since they may reduce hepatocyte apoptosis, regulate the inflammatory response, and encourage liver regeneration. In a mouse model of chronic liver damage caused by CCl4, exosomes were suggested to mitigate hepatic inflammation and collagen deposition.[504] Additionally, in mice models of CCl4-induced acute liver damage, exosomes generated hepatoprotective effects by increasing hepatocyte proliferation through enhanced proliferating cell nuclear antigen and high cell survivability. EVs also prevented hepatocyte apoptosis caused by APAP and H_2O_2 by upregulating the expression of the Bcl-xL protein.[505]

Human umbilical cord-derived MSCs (huc-MSCs) are a valuable asset in the field of regenerative medicine for treating liver

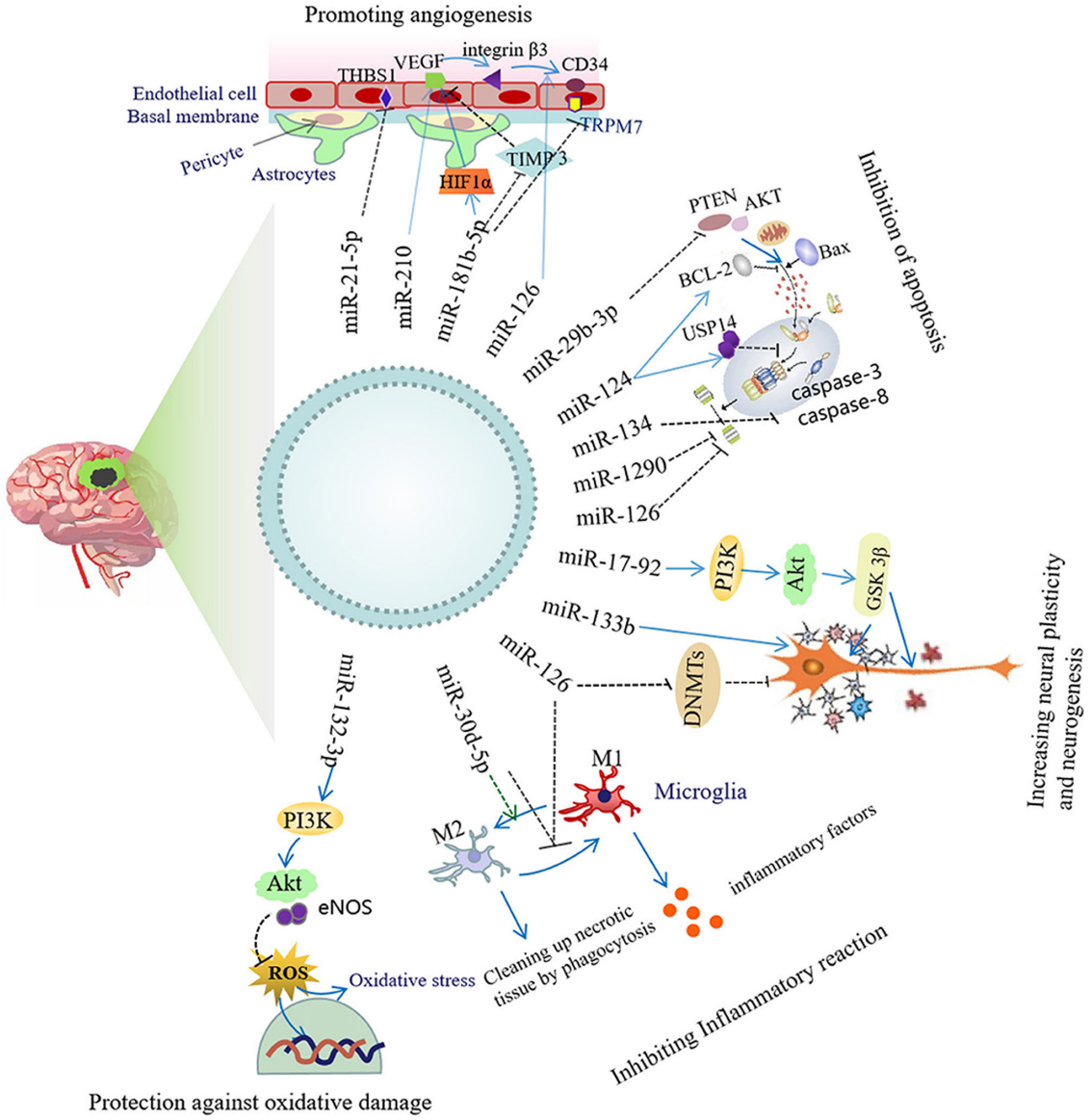

FIGURE 16 Neuroprotective mechanism of exosomal miRNA. Reprinted with permission from Xu et al.[479]

damage. These cells have been extensively studied in phase I and II clinical trials with the aim of enhancing liver function. Therefore, huc-MSC exosomes could be the best option for DILI. Apoptosis and reactive oxygen species were considerably reduced, as well as pro-inflammatory cytokines such as G-CSF, IL-1α, and MCP-1 after a single systemic injection of human MSC exosomes was given to patients with acute liver failure brought on by CCl4. Additional research revealed that huc-MSC exosomes prevented oxidative stress-induced apoptosis and stimulated ERK1/2 activation and Bcl2 expression. It is interesting to note that GPX1 knockdown hindered the function of huc-MSC exosome-induced liver recovery and for this reason, GPX1 is crucial for the antioxidant activity and liver protection provided by huc-MSC exosomes.[486] In comparison with the Bifendate group, which is often employed in clinical therapy to mitigate liver damage caused by CCl4, the huc-MSC exosomes group exhibited better integrated hepatic tissue structure and a reduced loss of hepatic lobules.[506] Thus, the current research showed that huc-MSC exosomes had a hepatoprotective effect against the development of liver damage.

4.3.3 | Therapeutic intervention for hepatocellular carcinoma

The sixth most prevalent cancer, and the one with the highest death rate, is hepatocellular carcinoma (HCC). EVs have been utilized in various trials to treat HCC cells. Hepatic stellate cells, stem cells, HCC cells, hepatocytes, and fat-free milk from cows are a few examples of several sources of EVs. The bulk of research involved loading miRNA, or other therapeutic compounds, into EVs by using an endogenous loading technique. Before EV shedding, the target donor cells are altered using the endogenous loading technique, also

TABLE 15 Mesenchymal stromal cells (MSCs) derived molecules (e.g., exosome) in liver failure preclinical models, especially acute liver failure (ALF).

Sources	Model	Intervention	Result (reference)
Umbilical cord	Mice	MSCs exosome	GPX1-enriched exosomes diminished oxidative stress and also apoptosis[486]
Placenta	Rat	MSCs exosome	CRP-enriched exosome provoked angiogenesis by upregulation of Wnt signaling axis[487]
Bone marrow	Rat	MSCs exosome	Stimulation of hepatoprotective impacts by exosome-rich fractionated secretome[488]
Bone marrow	Mice	MSCs exosome	Suppression of NLRP3 in macrophages and thereby reducing ALF by TNF-α pretreated exosome[489]
Menstrual blood	Mice	MSCs exosome	Liver function recovery, improved survival rates, and suppressed hepatocellular apoptosis[490]
Umbilical cord	Mice	MSCs extracellular vesicles	Inhibition of T-cell activation in liver tissue following reserve of CD154 expression[491]
Bone marrow	Mice	MSCs-conditioned medium	Promoting hepatocyte proliferation, inhibition of their apoptosis, hindrance of the infiltration of macrophages, improving Th2/Th1 ratio, and enabling hepatic stellate cell (HSC) loss[492]
Bone marrow	Rat	MSCs-conditioned medium	Marked attenuation of panlobular immune cells infiltrates and also hepatocellular apoptosis[493]
ESCs-MSCs	Mice	MSCs-conditioned medium	Supporting hepatocyte growth by VEGF enriched conditioned medium[494]
Bone marrow	Mice	MSCs-exosome	Attenuation of liver inflammation by exosomal miR-20a-5p/intracellular CXCL8 axis[495]
Bone marrow	Rat	MSCs-conditioned medium	Reduced hepatocyte apoptosis[496]
Bone marrow	Rat	MSCs-conditioned medium	Improving the hepatoprotective impacts of the conditioned medium by SMGO potently elicited through inhibition of inflammation and loss of hepatocytes[497]
Amniotic fluid	Mice	MSCs-conditioned medium	Hepatic progenitor-like (HPL)-CM showed superiority over amniotic fluid-MSCs in terms of liver recovery[498]

Note: Reprinted with permission from Shokravi et al.[485]

Abbreviations: CM, conditioned medium; CRP, C-reactive protein; ESCs, embryonic stem cells; GPX1, glutathione peroxidase1; IL-8 or CXCL8, interleukin 8; NLRP3, NLR family pyrin domain-containing 3; SMGO, silica magnetic graphene oxide; Th1/2, T helper 1/2; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

known as preloading.[507,508] Following the loading of therapeutic compounds into the donor cells, EV transference into the recipient HCC cell is made possible by coculturing the donor and recipient HCC cells. Every study so far has shown that their therapeutic payload can be delivered to target tumor cells and promote apoptosis in those cells,[509] lessen the chemoresistance,[510] inhibit cellular proliferation,[509,511–513] and decrease the movement of cells.[511]

In another study, recipient HCC cells were cocultured with donor HCC cells that had been transfected with genes encoding the sodium iodide symporter (NIS).[514] The NIS protein increased the sensitivity of transplanted HCC to I-131 ablation by increasing the toxicity of I-131 in those cells.[514]

In various animal models, HCC xenograft tumors have been subcutaneously implanted into various animals in immunocompromised mouse models. The EVs were loaded with antitumoral molecules and intravenously injected via tail veins or via direct intratumoral injections. The therapeutic EVs resulted in reduced tumor diameters,[509–511,515–519] enhanced apoptosis of tumor cells,[509–511,515] as well as enhanced chemoresistance.[510,516]

Apart from their function as therapeutic cargo, EVs have also been found to have an indirect application in the treatment of HCC. It has been shown that intraperitoneal injections of propofol stimulated tumor-associated macrophages to create miR-142-3p EVs, which is linked to a reduction in tumor development.[518] In one research study, mice with xenograft HCC were treated with an exosome-based tumor vaccination (dendritic cells triggered by tumor EVs).[519] The outcome showed that the xenograft tumor volume was successfully reduced by intravenous injection of an exosome-based tumor vaccination.[519] Because EVs may transfer therapeutic compounds into xenograft HCC, reducing tumor development, all existing in vivo investigations displayed the potential benefits of EVs as a therapeutic modality for HCC. EVs can also be utilized as a therapeutic cargo or as a tumor vaccination.

An article by Nimitrungtawee et al.[520] concluded that increasing data demonstrates the ability of HCC cells to communicate with one another using EVs in order to stimulate cell proliferation. Clinical research has previously shown that RNA cargo from HCC-derived EVs may serve as prospective serum biomarkers to aid in the diagnosis of

HCC. A portion of this EV-RNA is also linked to tumor size, suggesting that it might be used as a prognostic marker. Furthermore, data from research conducted in vivo and in vitro suggested that EVs may be used to reduce tumor size and development. A summary of the potential roles of EVs is shown in Figure 17.

4.3.4 | Viral and alcohol-induced hepatitis and cirrhosis

Liver illnesses, including viral hepatitis, alcoholic hepatitis and cirrhosis, nonalcoholic steatohepatitis, and hepatocellular carcinoma, impose a significant burden on many individuals globally. Worldwide, liver illnesses claim the lives of over 2 million individuals each year. The main causes of these deaths are hepatocellular carcinoma (HCC), complications from liver cirrhosis, and viral hepatitis (VH).[521]

A study by Zhou et al.[521] focused on immune cell exosomes and their effects on liver disease treatments examining both the pathogenic and possible therapeutic functions of these exosomes in liver illnesses. Although the authors discussed the potential use of exosomes produced from different immune cell sources to treat liver disease, further study is necessary, particularly in human subjects. Nevertheless, many benefits associated with exosomes have been found across a wide range of liver-related illnesses.

4.4 | Kidneys

Acute kidney injury (AKI) is a severe global issue that causes abrupt loss of renal function as a result of tissue destruction and then progresses to chronic kidney disease. It has a high incidence of morbidity and death. Numerous assaults, including nephrotoxic drugs, environmental toxins, ischemia, systemic inflammation, nephritis, and urinary tract obstruction, may cause AKI.[522] While research into viable treatments for AKI is ongoing, at this time, only simple supportive therapy is available. Regenerative medicine for kidney illnesses is not yet possible due to the multiple etiologies of renal damage and the significant complexity of the kidney structure. Nonetheless, modern stem cell treatments have been utilized in several preclinical models and clinical studies over the last few decades due to the immense promise that stem cell technology has demonstrated.[523–525] More significantly, EVs made from stem cells have attracted much more attention as a novel

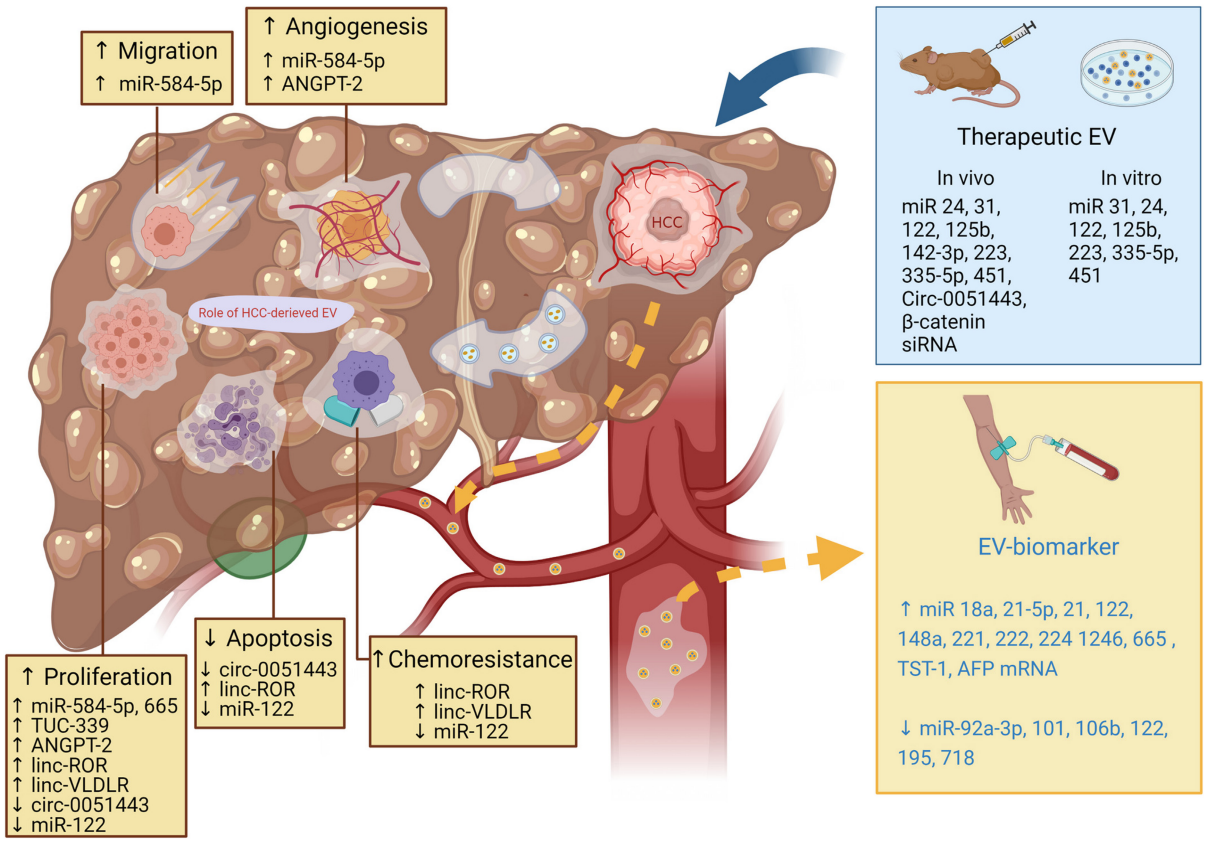

FIGURE 17 Roles of HCC-derived EVs, HCC-derived EVs as a biomarker, and the evidence of therapeutic EVs from currently available reports. HCC cells secrete EVs that can lead to increased tumor cell proliferation, migration, chemoresistance, and decreased tumor cell apoptosis. They can also affect tumor microenvironments such as increased angiogenesis. Some of these HCC-derived EVs can be detected in circulation, making them available for use as a diagnostic biomarker. Moreover, it is possible for EVs to be used as a therapeutic cargo to transfer therapeutic molecules into tumor cells. Several in vitro and in vivo reports have demonstrated antitumoral effects using this method. ANGPT2, angiopoietin2; Circ, circular RNA; linc, long interceding/intergenic non-coding RNA; miR, microRNA; siRNA, signal interference RNA; TUC, tumor ultra-conserved RNA. Reprinted with permission from Nimitrungtawee et al.[520]

therapeutic alternative for improved healing from many kinds of kidney damage without requiring allogeneic stem cells.[526]

In addition to their therapeutic possibilities, exosomes have also been studied for their potential as biomarkers for the identification of AKI.[527] A research paper titled: "Unconscious Cells and Sudden Kidney Damage: Potential Therapeutic Avenue for Renal Repair and Regeneration"[528] highlighted the effects of exosomes and how they affect multiple pathways of tissue regeneration including their role in (1) attenuating inflammation and improving immune modulation, (2) aiding in cell proliferation, (3) improving oxidative stress, (4) autophagy, and (5) minimizing cell death. Multiple lines of evidence substantiate the renoprotective impact of EVs derived from various sources in mitigating renal injury in diverse experimental models of AKI as presented in Table 16.[528]

4.4.1 | Bone marrow MSC-derived EVs for kidney therapy

A number of AKI models have shown the protective function of EVs produced from BMSCs. Bruno et al.[529] demonstrated that by transporting certain cellular mRNAs, human BMSC-derived EVs enhanced the growth and minimized apoptosis of renal proximal tubular cells and helped mice recover from glycerol-induced AKI. Additionally, by reducing inflammation and apoptosis, a single injection of BMSC-EVs soon after an ischemia–reperfusion (I/R) damage-induced acute kidney injury promoted kidney recovery and enhanced function.[530,531] Collino et al.[534] showed that miRNAs transported by BMSC-EVs played a significant role in the recovery process after AKI. Specifically, miR-199a-3p from BMSC-EVs inhibits the Akt and Erk1/2 signaling pathways to prevent renal I/R damage and apoptosis.[535] BMSC-EVs also improved renal function and morphological abnormalities in AKI produced by gentamicin or cisplatin.[532,533] Importantly, Gregorini et al.[559] showed that by modifying the expression of genes involved in membrane transport and cell energy metabolism, the immediate pretransplantation incubation of donated rat kidneys with BMSC-derived EVs decreased ischemia damage.[559]

4.4.2 | Umbilical cord MSC-derived EVs for kidney therapy

In many AKI models, the administration of EVs generated from umbilical cord MSC (UC-MSC) was useful in the treatment of kidney injury. In rats, UC-MSC-EVs injected underneath the renal capsule prevented cisplatin-induced AKI.[536] In vitro and in vivo cell proliferation was promoted by injecting UC-MSC-EVs, which also reduced oxidative stress and apoptosis.[536] Additionally, UC-MSC-EVs enhanced kidney function in vivo and reduced renal NRK-52E cell production of caspase 3 and the p38/MAPK pathway activation in vitro.[536] UC-MSC-derived EVs also provided protection against kidney damage, inflammation, and apoptosis caused by cisplatin.[543] In addition to enhancing renal function, UC-MSC-derived EVs demonstrated protection against sepsis-induced AKI by reducing tubular cell death and inflammation. In particular, NF-κB inhibition and miR-146b overexpression in renal tubular cells mediated the protective effects of EVs.[133] Interestingly, UC-MSC-EVs also prevented inflammation, apoptosis, and kidney damage in rats after I/R by suppressing CX3CL1 and reducing macrophage accumulation,[537] and also demonstrated antioxidative qualities.[540] Evidence from recent research suggests that UC-MSC-derived EVs control kidney angiogenesis in a way that is independent of HIF-1. This suggests that these EVs enhance kidney function after unilateral I/R by decreasing apoptosis and increasing proliferation and angiogenesis.[542] The pro-angiogenic payload of EVs, which includes RNAs and VEGF, may account for their capacity for regeneration.[542] Additionally, UC-MSC-EVs accelerate tubular cell dedifferentiation and proliferation by upregulating HGF expression. This is probably due to the EVs' stimulation of Erk1/2 signaling while transferring RNA to damaged tubular cells.[538]

Through the use of miR-30b/c/d, human UC-MSC-derived EVs prevented I/R-induced kidney damage by preventing mitochondrial fragmentation and lowering apoptosis,[539] as well as miR-125b-5p/p53,[545] stimulation of the Nrf2/ARE system,[541] and OCT-4-mediated Snail pathway recruitment in RPTECs.[544] According to in vivo imaging data, EVs preferred to settle near renal proximal tubular cells in ischemia-injured kidneys.[545]

4.4.3 | Placental tissue MSC-derived EVs for kidney therapy

Liu et al.[548] examined the function of EVs produced from human placental MSC (hP-MSC) in AKI and demonstrated that they had a greater impact when encapsulated in a collagen matrix prior to intrarenal delivery. The collagen matrix promoted renal tubular cell proliferation and angiogenesis while preventing apoptosis and endoplasmic reticulum stress. It also enhanced the retention and therapeutic efficiency of hP-MSC-EVs in I/R-induced AKI.[548] Similarly, Zhang et al.[549] created hydrogels known as RGD (Arg-Gly-Asp) to control the stability and retention of the EVs. RGD bound to integrins on the surface of the MSC-EV membrane mediated the interaction between EVs and hydrogel. In I/R-induced AKI, EV-RGD hydrogels effectively prevented renal damage and reduced their morphological damage by encouraging autophagy and proliferation in tubular epithelial cells.[549]

4.4.4 | Adipose tissue MSC-derived EVs for kidney therapy

Adipose MSC-derived EVs (ADSC-EVs) have also been studied in relation to AKI recovery and regeneration. ADSC-EVs significantly reduced oxidative stress, apoptosis, and inflammation while also promoting renal angiogenesis thereby improving kidney dysfunction from I/R damage. An even better result than with EVs alone

TABLE 16 Application of EVs as therapeutic agents in acute kidney injury.

EV source	AKI model	EV cargo	Signaling pathway	Mechanism	Administration	References
BMSCs	Glycerol	mRNA	n/i	Proliferation, apoptosis	Intravenous	529
	I/R injury	RNA	n/i	Proliferation, apoptosis	Intravenous	530
	I/R injury	CCR2	NF-κB p65	Inflammation	Intravenous	531
	Cisplatin	n/i	n/i	Proliferation, apoptosis	Intravenous	532
	Gentamicin	RNA	n/i	Proliferation, apoptosis	Intravenous	533
	Glycerol	miRNA	n/i	Inflammation	Intravenous	534
	I/R injury	miR-199a-3p	Akt, Erk1/2	Apoptosis	Intravenous	535
UC-MSCs	Cisplatin	n/i	p38/MAPK, Erk1/2	Oxidative stress, apoptosis, proliferation	Renal capsule	536
	I/R injury	n/i	CX3CL1	Apoptosis, inflammation	Intravenous	537
	I/R injury	HGF/RNA	Erk1/2	Proliferation, apoptosis	Intravenous	538
	I/R injury	miR-30b/c/d	n/i	Apoptosis	Intravenous	539
	I/R injury	n/i	NOX2/gp91	Oxidative stress, apoptosis, proliferation	Intravenous	540
	I/R injury	n/i	Nrf2/ARE	Oxidative stress, apoptosis	Intravenous	541
	I/R injury	VEGF, RNAs	n/i	Apoptosis, proliferation, angiogenesis	Intravenous	542
	Cisplatin	n/i	n/i	Inflammation, apoptosis, autophagy	Renal capsule	543
	I/R injury	Oct-4	Snail	Apoptosis, proliferation	Intravenous	544
	Sepsis	miR-146b	NF-κB	Apoptosis, inflammation	Intravenous	133
	I/R injury	miR125b-5p	p53	Apoptosis, proliferation	Intravenous	545
AD-MSCs	I/R injury	n/i	n/s	Inflammation, apoptosis, oxidative stress, angiogenesis	Intravenous	546
	Sepsis	n/s	SIRT1	Apoptosis, inflammation	Intravenous	547
P-MSCs	I/R injury	n/i	n/i	Proliferation, angiogenesis, apoptosis	Intrarenal	548
	I/R injury	Let-7a-5p	n/i	Proliferation, apoptosis, autophagy	Intrarenal	549
K-MSCs	I/R injury	mRNA	n/i	Proliferation, angiogenesis	Intravenous	550
	I/R injury	miRNAs	n/i	Proliferation	Intravenous	551
L-MSCs	Glycerol	n/i	n/i	Proliferation, apoptosis	Intravenous	552
u-EVs	Glycerol	miRNA, Klotho	n/i	Proliferation, inflammation	Intravenous	553
TECs	I/R injury	CD26	p53, p21	Proliferation, inflammation	Intravenous	554
USCs	I/R injury	miR-146a-5p	NF-κB	Apoptosis, inflammation	Intravenous	555
Mac	I/R injury	IL-10	mTOR	Inflammation, autophagy	Intravenous	556
EPCs	I/R injury	miRNAs	n/i	Proliferation, apoptosis	Intravenous	557
	Sepsis	miR-93-5p	H3K27me3/TNF-α	Inflammation, apoptosis	Intravenous	558

Note: Reprinted with permission from Kosanovic et al.[528]

Abbreviations: AD-MSCs, adipose tissue MSCs; AKI, acute kidney injury; ARE, antioxidant response element; BMSCs, bone marrow MSCs; EPCs, endothelial progenitor cells; EVs, extracellular vesicles; I/R, ischemia–reperfusion; K-MSCs, kidney resident MSCs; L-MSCs, liver resident MSCs; Mac, macrophages; MAPK, mitogen-activated protein kinase; MSCs, mesenchymal stem cells; mTOR, mammalian target of rapamycin; n/i, not investigated; n/s, not specifiedP-MSCs, placental MSCs; TECs, tubular epithelial cells; UC-MSCs, umbilical cord MSCs; uEVs, renal derived EVs isolated from urine; USCs, urine-derived stem cells; VEGF, vascular endothelial growth factor.

was obtained when ADSCs and ADSC-EVs were used in combination.[546] Through the SIRT1 signaling pathway, ADSC-derived EVs reduced renal inflammation and apoptosis in a sepsis-induced AKI model.[547]

4.4.5 | EVs derived from other sources for kidney therapy

There is growing evidence that EVs produced from macrophages, kidney MSCs, liver MSCs, tubular epithelial cells, or endothelial progenitor cells (EPCs) are advantageous in experimental AKI.

In I/R-induced AKI, kidney-derived MSC-EVs were shown to enhance kidney function and structural alterations by transferring mRNA with pro-angiogenic characteristics, which in turn promoted the proliferation of peritubular capillary endothelial cells and prevented the loss of peritubular microvessels.[550] Glomerular-MSC-EVs activated cell proliferation and transferred miRNA cargo to protect against I/R-induced AKI.[551] Additionally, CD26-containing tubular epithelial cell-derived EVs reduced inflammation and promoted cell proliferation by lowering p53 and p21, therefore mitigating I/R-induced AKI.[554]

It is interesting to note that EVs produced from human urine stem cells (USCs) prevented I/R-induced AKI and reduced inflammation and apoptosis by transferring miR-146a-5p and consequently reducing NF-κB activation.[555] Similarly, EVs generated from liver MSCs ameliorated mice's glycerol-induced AKI.[552] Normal urine-derived EVs from kidneys (uEVs) were shown to enhance the recovery from glycerol-induced AKI by promoting tubular cell proliferation, re-establishing endogenous Klotho levels, and reducing inflammation via miRNA cargo and Klotho transfer to resident kidney cells.[553]

EPC-secreted EVs stimulated renal regeneration in I/R-induced AKI by delivering miRNA cargo to local tubular epithelial cells and thus triggering regenerative mechanisms.[557] In addition, EVs released by EPCs containing miR-93-5p were shown to provide protection against sepsis-induced AKI by reducing vascular leakage, inflammation, and apoptosis. This protective effect was achieved via the modulation of the H3K27me3/TNF-axis.[558]

Ultimately, when EVs obtained from macrophages were loaded with IL-10, it led to a successful delivery to renal tubular cells and macrophages in damaged kidneys and improved durability of vesicles. This process helped alleviate kidney injury, suppress inflammation, and stimulate mitophagy by inhibiting mTOR signaling.[556]

At present, a list of clinical trials is found on www.clinicaltrials.gov investigating the use of exosomes for treating various kidney related illnesses. Exosomes and EVs generated from umbilical cord MSCs were shown in a phase II/III clinical trial to be effective in treating chronic kidney disease and slowing disease progression. Serum creatinine, blood urea, and urine albumin creatinine ratio were significantly improved in patients with stage III and IV chronic renal disease who received eGFR-EVs made from cord tissue MSC.[560]

4.4.6 | MSC-Exos for chronic kidney disease

Chronic kidney disease (CKD) affects 10% of the population globally with many patients unaware of their condition.[561] While the etiology of CKD may differ, diabetes and hypertension remain the predominant factors.[561] Regardless of the many factors that contribute to the initial kidney damage, the development of renal fibrosis is a shared characteristic of all types of CKD.[562]

In experimental CKD, MSCs have shown encouraging effectiveness in reducing kidney damage.[563,564] MSC-Exos, which share repair capabilities with MSCs, have been extensively used in the treatment of CKD, including DKD and renal fibrosis. The preclinical experiments included numerous CKD animal models, varied doses and timings, and several delivery techniques (tail infusion, organ perfusion, or direct application in the kidney), yet each study showed promising outcomes when utilizing EVs/exosomes.

4.4.7 | MSC-Exos for diabetic kidney disease

Chronic kidney disease (CKD), a consequence of diabetes mellitus (DM) affecting small blood vessels, is the most prevalent type of CKD and is expected to rise significantly worldwide.[561] Microalbuminuria is a common early sign in DKD, but it may not always occur, and it consequently indicates a higher likelihood of developing kidney damage over time. Diabetic individuals with renal disease have a higher risk of death compared to those without renal impairment. Given the projected rise in the worldwide adult population affected by DM, from 8.8% in 2015 to 10.4% in 2040, the significance of DKD and need for therapeutic options to manage or treat the disease is eminently needed.[561]

Hyperglycemia induces the activation of various inflammatory pathways through several mechanisms, including the direct generation of reactive oxygen species, oxidative stress, stimulation of the renin-angiotensin-aldosterone system (RAAS), secretion of profibrotic cytokines like TGF-beta, and formation of advanced glycation end-products.[565] All of these result in albuminuria, podocyte and tubular damage, and apoptosis. Progressive fibrosis results from the accumulation of ECM proteins, including collagen and fibronectin, in the tubulointerstitium and renal mesangium due to an increase in matrix protein synthesis and a reduction in protein breakdown.[565,566] The potential therapeutic effects of MSC-Exos in STZ-DKD has been quite frequently investigated using in vivo models of the disease (mice or rats) as well as in vitro podocyte, tubular epithelial cell (TEC), and glomerular endothelial cells. The effectiveness of MSC-Exos in alleviating DKD in preclinical models is highlighted in Table 17.

4.4.8 | MSC-Exos for kidney fibrosis

Commonly, kidney fibrosis, namely tubulointerstitial fibrosis, is the ultimate result of almost all progressive forms of chronic kidney

TABLE 17 Summary of therapeutic effects of MSC-Exos from various sources in preclinical models of DKD.

MSC source	Model	Dose	Administration	Effects	Mechanism of action	References
Rat bone marrow	In vivo: STZ-induced DKD	Single: 5.3×10^7	Renal Subcapsular	↓ Renal tubule expansion, vacuolation, tubular atrophy ↓ Degeneration	↓ TGF-β ZO-1 was maintained ↓ Inflammatory cell Infiltration	566
	In vitro: Primary TECs	Not stated	Co-culture	↓ Degeneration ↓ Apoptosis		
Rat bone marrow	STZ-induced DKD	100 μg/kg once per day × 4 weeks	Intravenous (tail vein)	↑ Autophagy: ↑ LC3-II/LC-I, p62, Beclin-1 ↓ BUN, Scr, Glu, proteinuria at 10 and 12 weeks ↓ Fibrosis	↓ mTOR, S6K1, p62 ↓ Collagen, FN ↓ TGF-β	568
Mouse adipose	In vivo: Spontaneous diabetes	Single: not stated, 12-week therapy	Intravenous (tail vein)	↓ BUN, creatinine, proteinuria ↑ Autophagy ↓ Podocyte apoptosis	↑ miR-486 ↓ Smad1/mTOR activation ↓ Cleaved caspase 3	569
	In vitro: HG-treated MPC5	25 μg/mL for 48 h	Co-culture	↑ Cell viability ↓ Apoptosis		
Mouse adipose	In vitro: HG-treated MPC5	Not stated	Co-culture	↓ Podocyte EMT ↑ miR-215-5p, -879-5p, -3066-5p, -7a-5p	↓ ZEB2 transcription	570
Adipose	In vivo: STZ-induced DKD	50 μg twice weekly × 3	Intravenous (caudal vein)	↓ Glu, Scr, UACR, kidney/body weight ↓ Mesangial hyperplasia ↓ Kidney fibrosis	Delivery of miR-125a ↓ HDAC1, ET-1	571
	In vitro: HG-treated rat GMC	Not stated	Co-culture	↓ IL-6, Col I and FN ↑ Bcl-2 and Bax		
Human umbilical cord	In vitro: HG-treated HK2, NRK-52E and hrGECs	25, 50, and 100 μg/mL for 24 h	Co-culture	↓ TGF-β, IL-6, IL-1β, and TNF-α	Secretion of EGF, FGF, HGF, and VEGF	572
Human urine	In vivo: STZ-induced DKD	Multiple: 100 μg weekly × 12	Intravenous (tail vein)	↓ Urine volume, albuminuria ↓ Apoptosis of podocyte and tubular cells ↑ Glomerular endothelial cell proliferation ↑ Angiogenesis	↓ Caspase-3 Delivery of VEGF, TGF-β 1, angiogenin, BMP-7	573
	In vitro: HG-treated immortalized human podocytes	5, 10, and 50 μg/mL for 72 h	Co-culture	↓ Podocyte apoptosis		

TABLE 17 (Continued)

MSC source	Model	Dose	Administration	Effects	Mechanism of action	References
Human urine	In vivo: STZ-induced DKD	100 μg once weekly × 12	Intravenous (tail vein)	↓ Glu, KW, BUN, Scr, Ucr ↓ Podocyte injury ↓ Apoptosis	↓ VEGFA, MCP-1, TGF-β1 and TNF-α ↓ Bax and Caspase-3	574
	In vitro: HG-treated human podocytes		Co-culture	↑ Cell viability ↓ Apoptosis		

Note: Reprinted with permission from Cao et al.[567]

Abbreviations: AD-MSCs, adipose-derived mesenchymal stem cells; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BMP-7, bone morphogenetic protein-7; BUN, blood urea nitrogen; CK1d, casein kinase 1d; COL1, collagen-1; DKD, diabetic kidney disease; EMT, epithelial–mesenchymal transition; ET-1, endothelin-1; FGF, fibroblast growth factors; FN, fibronectin; Glu, blood glucose; GMC, glomerular mesangial cell; GSH, glutathione; HDAC1, histone deacetylase 1; HG, high glucose; HGF, hepatocyte growth factor; IL-6, interleukin-6; KW, kidney weight; LC3, microtubule-associated protein light chain 3; MCP-1, monocyte chemoattractant protein-1; miR, microRNA; MSC, mesenchymal stem cells; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species; S6K1, ribosomal protein S6 kinase beta-1; Scr, serum creatinine; STZ, streptozotocin; TGF-β, transforming growth factor-β; TECs, tubular epithelial cells; TGF-βR1, transforming growth factor-β type 1 receptor; TNF-α, tumor necrosis factor-α; Ucr, urine creatinine; VEGF, vascular endothelial growth factor; ZO-1, tight junction protein 1; 2K-1C, 2 kidneys, 1 clip model.

disease.[562] Tubulointerstitial fibrosis histology is distinguished by the accumulation of extracellular matrix in the interstitium. This accumulation is associated with damage to tubular cells, activation and proliferation of fibroblasts, and a decrease in the density of blood vessels surrounding the tubules.[562] Through a variety of pathways, TGF-beta has been shown to be a key profibrotic factor in several investigations.[575]

Recently, the antifibrotic efficacy of MSC-Exos has been assessed using a variety of rodent models of CKD, including diabetic and hypertensive CKD models, and ischemia–reperfusion injury (Table 18). Unilateral ureteral obstruction causes significant renal damage, which manifests as decreased glomerular filtration rate and renal blood flow within 24 h. Interstitial inflammation peaks 2–3 days later, and tubular dilatation, tubular atrophy, and fibrosis appear a week later. It results in severe interstitial renal fibrosis with excessive ECM buildup, tubular cell death, resident renal cell phenotypic change, and macrophage infiltration into the interstitial space.[576] Table 18 summarizes the use of MSC-Exos from various sources on antifibrotic effects in kidney fibrosis.

4.5 | Ovaries

While not as commonly investigated as some of the other organs, ovaries have also been a target of exosome-related therapies. In a study titled: "Mesenchymal stem cells therapy: An auspicious approach for the management of uterine scarring and early ovarian failure," Gao and colleagues investigated stem cells from various sources and their impact on ovarian regeneration and improvements in scarring.[583] While most of the research to date has been on stem cells, few studies have investigated exosomes with the authors hinting at their low immunogenicity as a key advantage. According to a study by Yang et al., exosomes produced by BMSCs considerably improved the estrous cycle, augmented the quantity of basal and sinus follicles, and modulated the levels of reproductive hormones in rats suffering from premature ovarian failure. The enhancement was linked to the suppression of cell death in granulosa cells by specifically targeting phosphatase and tensin homologs.[584] Moreover, the existence of miRNAs in BMSC-derived Exos might play a significant role in their ability to resist fibrosis while repairing intrauterine adhesions in the endometrium.[585,586] Exosomes have the potential to cure a variety of ovarian illnesses, albeit research in this area of medicine remains in its early stages.[583]

5 | DEGENERATIVE PROCESSES

While many of the upcoming sections could certainly be attributed to the degeneration of tissues, this section focuses specifically on long-term degeneration tissues and their common diseases. Exosomes have played an important role in their improvements. These sections include primarily the effects of type 2 diabetes on the body as well as the number of issues related to respiratory disease/degeneration

TABLE 18 Summary of antifibrotic effects of MSC-Exos from various sources in preclinical models of kidney fibrosis.

MSC source	Model	Dose	Administration	Effects	Mechanism of action	References
Human umbilical cord	In vivo: UUO In vitro: NRK52E incubated with TGF-β	Single: 200 μg Not stated	Left renal artery Co-incubation with isolated exosome	↑Renal function (↓ Scr, BUN) ↓ Tubular injury ↓ Tubulointerstitial fibrosis ↓ Apoptosis ↑proliferation ↓ Oxidative stress ↓ Apoptosis ↑Proliferation ↓ Oxidative stress	↓ ROS-mediated p38 MAPK/ERK signaling pathway ↓ Bax, cleaved caspase-3 ↓ ROS, MDA ↑ antioxidants: GSH	577
Human bone marrow	In vivo: UUO In vitro: NRK52E incubated with TGF-β	Single: Released from 1×10^6 MSCs Not stated	Intravenous Co-incubation with isolated exosome	Exosomes home to injured kidneys ↓ Fibrosis ↓ Fibrosis	Delivery of miR-let7c ↓ Collagen, MMP-9, α-SMA, TGF-βR1	559
Human bone marrow (transfected with anti-let-7i-5p)	In vivo: UUO In vitro: NRK52E incubated with TGF-β	Single: 1 mg/kg Not stated	Intravenous MSC on Transwell with NRK52E grown on the lower chamber	↑Renal function (↓ BUN, ↓ Scr, ↓ Ucr, ↑eGFR) ↓ Fibrosis ↓ TGF-β1-induced fibrogenic responses ↓ EMT	↓ Let-7i-5p ↓ Collagen, FN, α-SMA, ↑TSC1 ↓ Phosphorylation of mTORC1, p70S6K and 4E-BP1	578
Human umbilical cord	In vivo: UUO	Single: 200 μg	Intravenous	↓ Tubulointerstitial fibrosis	Exosomes delivered CK1 1δ and β-TRCP to degrade YAP	579
Adipose (transfected with GDNF)	In vivo: UUO In vitro: HUVEC against H/SD	Single: 200 μg Single: 100 μg/mL	Caudal vein Co-incubation with isolated exosome	↓ PTC rarefaction ↓ Tubulointerstitial fibrosis ↑ Endothelial function, angiogenesis ↓ HUVEC injury ↓ Apoptosis ↑Endothelial angiogenesis	↑SIRT1/p-eNOS ↓ α-SMA ↑ VEGF, ↓ HIF-1α	580
Adipose	In vivo: IRI In vitro: primary TECs stimulated with TGF-β	Single: 100 μg Not stated	Caudal vein Co-incubation with isolated exosome	↑ Tubular proliferation, regeneration ↓ Interstitial fibrosis ↓ Inflammation ↓ TGF-β1-induced transformation of TECs to pro-fibrotic phenotype	↑Sox9 ↓ α-SMA, PDGFR-β	581
Adipose	2K-1C Unilateral renal artery stenosis	Single: 100 μg	Caudal vein	↓ HIF-1α Stabilized systolic blood pressure ↑ Natriuresis ↓ Fibrosis ↓ Inflammation	↓ Collagen, TGF-β ↑ IL-10	582
Pluripotent stem cell	In vivo: UUO In vitro: NRK-52E	Single: 10^{11} particles/mL $10^6/10^7/10^8$ particles/m	Tail vein Co-incubation with isolated exosome	↓ Fibrosis ↓ Inflammation ↓ Col-1, α-SMA ↑E-cadherin	↑SIRT6 ↓ β-catenin	544

Note: Reprinted with permission from Cao et al.[567]

Abbreviations: AD-MSCs, adipose-derived mesenchymal stem cells; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; BMP-7, bone morphogenetic protein-7; BUN, blood urea nitrogen; CK1d, casein kinase 1d; COL-1, collagen-1; DKD, diabetic kidney disease; EMT, epithelial–mesenchymal transition; ET-1, endothelin-1; FGF, fibroblast growth factors; FN, fibronectin; GDNF, glial-derived neurotrophic factor; GMC, glomerular mesangial cell; GSH, glutathione; HDAC1, histone deacetylase 1; HG, high glucose; HGF, hepatocyte growth factor; H/SD, hypoxia/serum deprivation; HUVECs, human umbilical vein endothelial cells; IL-6, interleukin-6; IRI, ischemia/reperfusion injury; LC3, microtubule-associated protein light chain 3; miR, microRNA; KW, kidney weight; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MSC, mesenchymal stem cells; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; PDGFR-β, platelet-derived growth factor receptor beta; ROS, reactive oxygen species; S6K1, ribosomal protein S6 kinase beta-1; Scr, serum creatinine; SIRT1, sirtuin-1; Sox9, SRY-box transcription factor 9; STZ, streptozotocin; TECs, tubular epithelial cells; TGF-β, transforming growth factor-β; TGF-βR1, transforming growth factor-β type 1 receptor; TNF-α, tumor necrosis factor-α; Ucr, urine creatinine; VEGF, vascular endothelial growth factor; ZO-1, tight junction protein-1; 2K-1C, 2 kidneys, 1 clip model; YAP, yes-associated protein; UUO, unilateral ureteral obstruction.

over time. Exosomes have played a marked impact on the improvement of all tissues, as highlighted below.

5.1 | Type 2 diabetes mellitus

Many review articles have been written on the use of exosomes in the treatment of type 2 diabetes mellitus.[587,588] Globally, the incidence of diabetes mellitus (DM) is rising at an alarming pace. More than 30.3 million people in the United States suffer from DM and 91.2% of them are type 2 diabetes mellitus (T2DM), which disproportionately affects African Americans and Hispanics. T2DM is the primary cause of morbidity and death for diabetic individuals and a significant risk factor for cardiovascular disease (CVD). Intensive glucose control has not been able to stop the development of macro- and microvascular-associated mortality in this population, despite major advancements in T2DM therapy. This emphasizes the need to better understand the underlying molecular pathways that contribute to CVD in the context of type 2 diabetes. The development of vascular problems brought on by diabetes, such as diabetic nephropathy (DN) and CVD, is significantly influenced by endothelial dysfunction (ED). Furthermore, as the costs of managing and treating type 2 diabetes and its multisystem consequences continues to climb, the troubling rise in the disease's prevalence in the United States and other countries has put a heavy burden on healthcare systems, policymakers, families, and caregivers.

The intricate molecular foundations of type 2 diabetes and its associated consequences are made up of an interconnected system of lifestyle, genetic, and epigenetic variables that function within a physical, social, and cultural context.[589] In particular, it is generally believed that genetic predisposition, excessive energy-dense food intake, and inactivity cause T2DM by interfering with the feedback loops that regulate insulin action and secretion.[590] Persistent hyperglycemia may arise from this disturbance, which may also affect β-cell activity, insulin signaling, and glucose metabolism. Insulin resistance and β-cell dysfunction both arise early in the etiology of type 2 diabetes and, over time, propel the development of IGT from normal glucose tolerance (NGT) to T2DM.[589] Furthermore, the development of T2DM is influenced by several variables, such as population aging, intrauterine environment, alterations in the microbiota, and pollution.

5.1.1 | Exosomal miRNAs as markers of endothelial dysfunction

Exosomes may be detected in several body fluids, including blood, saliva, urine, tears, and lactation. This characteristic makes exosomes appealing as noninvasive biomarkers for the illness. Exosomes serve as distinctive markers of the cells they originate from and the physiological state of that cell.[591] Hence, the diverse concentrations of exosomes and their abundant payload, including as proteins, mRNAs, and miRNAs, may serve as valuable indicators for predicting and diagnosing diseases. Furthermore, it may provide a valuable understanding of the intricate biological mechanisms involved in disorders like type 2 diabetes, as well as the underlying endothelial dysfunction that contributes to the vascular problems associated with this metabolic disorder. Tables 19 and 20 demonstrate examples of commonly utilized exosomal miRNAs and microRNAs used as biomarkers. In fact, nowadays, various exosomes derived from various body fluid sources have now been utilized for the detection of DM and its subsequent disease (Table 21).

5.1.2 | Exosomes, glucose, and lipid metabolism

Changes in the metabolism and absorption of glucose is the primary issue in diabetes, ultimately resulting in hyperglycemia.[648] The ghrelin system has a role in improving glucose metabolism in the treatment of TIDM, and hyperbaric oxygen may influence the ghrelin system, hence impacting glucose metabolism.[649] Clinical investigations on diabetic individuals have shown that GLP-1 may have a function in lowering blood glucose levels.[650] Exosomes have been found to drastically reduce gluconeogenesis and promote the metabolism and absorption of fats and carbohydrates.[651] Notably in DM, autophagy suppression reduces the therapeutic effect of exosomes produced from MSCs. Further research showed that exosomes triggered AMP-activated protein kinase (AMPK) to increase autophagy by upregulating Beclin-1 and LC3-II, which in turn promoted lipid metabolism and glucose absorption.[651]

5.1.3 | Exosomes and β-cell function

The pancreas contains a large number of Langerhans islets, whereby each islet is made up of around 1000 β cells and weighs 0.9 g in total.[652] The β cells are affected in diabetes mellitus and obesity, among other diseases. Hyperinsulinemia, or elevated insulin levels in the plasma of obese patients, is a compensatory mechanism that keeps insulin resistance at bay. Thus, the mass of β cells increases, resulting in hyperinsulinemia.[653] An obese rat model demonstrated that obesity might increase β cell mass up to three fold.[654] TIDM is characterized by the loss of β cells or their inability to secrete insulin and the mass of β cells in TIDM patients has been shown to decline to nearly 100% over an extended period of time.[655–657]

MSC-Exos have been used in an attempt to treat TIDM. After the exosomes were injected intravenously into animal models, insulin and glucose levels were assessed 6 weeks later. According to the findings,[658] exosomes stimulated β-cell regeneration in the pancreas and increased their bulk which is crucial for increasing insulin release in type 1 diabetes. Apart from increasing insulin levels, MSC-Exos markedly reduced serum glucose levels.

TABLE 19 Extracellular miRNAs associated with type 2 diabetes mellitus and endothelial dysfunction.

miRNA	Normaglycemic	T2DM	Targets/pathways	Source	Complication	References
miR-126	Up	Down	SPRED-1 PIK3R2/p85-β-PLK4	Plasma	Impaired angiogenesis	592–594
miR-26a	Up	Down	TRPC6	Plasma	Impaired angiogenesis	595
miR-133b	Down	Up	MAPK/ERK signaling	Serum	Diabetic nephropathy	596,597
miR-342	Down	Up	SRY-box 6 (SOX-6)	Serum	Diabetic nephropathy	596,598
miR-30a	Down	Up	TGF-β 1 Becn1	Serum	Diabetic nephropathy	596,599
miR-326		Up	ADIPOR-2 (adiponectin)	Plasma	T2DM	600
Let-7a	Down		Glucose metabolism	Plasma	T2DM	600
Let-7f	Down		Glucose metabolism	Plasma	T2DM	600
miR-20b-5p	Down	Up	AKT-interacting protein	Serum	T2DM	601
miR-21-5p	Down	Up	WWP1 (WW domain-containing protein 1) Endothelial progenitor cell proliferation	Plasma	T2DM	602,603
miR-375-3p	Down	Up	β-cell function	Serum	T2DM	604
miR-362-3p	Down		ADAMTS1	Plasma	Atherosclerosis (CAD)	605
miR-15a	Down	Up	UCP-2	RBC	T2DM	606,607
miR-15b	Down	Up	TNF-alpha SOCS3	RBC	Pre-T2DM	606
miR-499	Down	Up	PTEN	RBC	Pre-T2DM	606
miR-7	Down	Up	mTOR signaling	Serum	Vascular complications	608
miR-25-3p		Up	CDH1 and PTEN	Plasma	Diabetic retinopathy	609
miR-320b	Down	Up	Angiogenesis	Plasma	Diabetic retinopathy	609
miR-495-3p	Down	Down		Plasma	Diabetic retinopathy	609
miR-34a	Down	Up	Sirt1	Mouse aortic endothelial cells	Endothelial dysfunction	610
miR-210	Down	Up	Cell proliferation	Serum	Diabetic retinopathy	611
miR-210	Up	Down	PTP1B	RBC	T2DM	612
miR-139-5p	Down	Up	c-Jun	Peripheral blood	T2DM	613

Note: Reprinted with permission from Fluitt et al.[588]

5.1.4 | Exosomes and insulin resistance

The management of patients with diabetes mellitus is becoming increasingly more difficult due to their insulin resistance, which causes a change in the insulin concentration–effect curve and a tendency for greater concentration levels to have a comparable effect.[658] Commonly seen in TIIDM and sometimes in obese individuals, insulin resistance is caused by cells that are not sensitive to insulin.

Insulin increases the expression and activity of GLUTs, including GLUT4, to improve the absorption of glucose by cells.[659] Nonetheless, there are a few causes of insulin resistance. For example, fat buildup in obese individuals causes a reduction in adipokine release, an increase in lipolysis, and the production of pro-inflammatory cytokines. These effects result in elevated amounts of free glycerol and fatty acids linked to insulin resistance.[660]

Exosomes have been shown in experiments to have therapeutic effects by increasing insulin sensitivity, a crucial aspect of treating diabetes mellitus. A high-fat diet, which includes fatty acids like palmitic acid (PA), may cause insulin resistance. High PA intake causes the hepatocytes to develop the insulin resistance characteristics. In addition to inhibiting IRS-2 phosphorylation and preventing glucose absorption as a consequence of insulin stimulation, the PA may cause apoptosis in INS-1 cells. The neutral ceramidase (NCDase)-enriched exosomes inhibit insulin resistance brought on by excessive PA consumption and halts the production of reactive oxygen species, perhaps helping to reduce INS-1 cell death.[661] In a different experiment, exosomes isolated from umbilical cord MSCs were used to treat TIIDM. The authors demonstrated the ability of exosomes to increase insulin-induced glucose absorption, lasting for at least 48 h. Additionally, exosomes lower leptin levels and dramatically increased SIRT1 and IRS-1 mRNA expression, demonstrating their ability to increase adipocyte insulin sensitivity.[662]

One of the most well-known cargos of exosomes are miRNAs, and the effect of exosomes on target cells will vary depending on

TABLE 20 Exosomal microRNAs associated with type 2 diabetes mellitus and endothelial dysfunction.

miRNA	Normaglycemic (concentration/ excretion)	T2DM (concentration/ excretion)	Targets/pathways	Source of exosomes	Method of isolation	Complication	References
miR-451	Low	High	YWHAZ CAB39	Urine	Ultra-centrifugation	Diabetic nephropathy	614–616
Let-7c-5p	Low	High		Urine	Differential centrifugation	Diabetic nephropathy	617
miR-192	Low	High	Egr1	Urine	Ultra-centrifugation	Diabetic nephropathy	618,619
Let-7e-5p	Low	High	FASLG (migration and tube formation of endothelial progenitor cells)	Urine	miRCURY™ exosome isolation kits (Qiagen)	Diabetic nephropathy	620–622
miR-15b	Low	High	TNF-alpha	Urine	Ultra-centrifugation	Diabetic nephropathy	623
miR-34a	Low	High	Growth arrest specific 1 (GAS1)				
miR-636	Low	High	Adipogenesis				
miR-30b-5p	Low	High	Epithelial-to-mesenchymal transition	Urine	Ultra-centrifugation	Diabetic nephropathy	620
miR-20-5p	Low	High	Wnt9b/β-catenin signaling pathway	Peripheral blood	Ultra-centrifugation	Wound healing angiogenesis	624,625
miR-126	Low	High	Angiogenesis vascular integrity	Mouse brain endothelial cells	ExoQuick-TC (exosome precipitation solution kit, system biosciences)	Stroke	454
miR-320c	Low	High	ADAMTS5 CDK6 TSP-4 BMP6	Urine	ExoQuick-TC (exosome precipitation solution kit, system biosciences)	Diabetic nephropathy	626
Let-7i-3p	Low	High	Wnt/b-catenin signaling cascade, activin receptor signaling, and cell differentiation and proliferation	Urine	miRCURY™ exosome isolation kits (Qiagen)	Diabetic nephropathy	627
miR-24-3p	Low	High				Diabetic nephropathy	
miR-27b-3p	Low	High				Diabetic nephropathy	
miR-15b-5p	High	Low				Diabetic nephropathy	
miR-25-3p	Low	High	Endothelial cell proliferation Angiogenesis	Plasma	ExoQuick-TC (exosome precipitation solution kit, system biosciences)	Diabetic retinopathy	609
miR-320b	Low	High					
miR-495-3p	Low	High					

Note: Reprinted with permission from Fluitt et al.[588]

TABLE 21 Exosomes derived from body fluid can act as novel biomarkers for early diagnosis of DM and diabetic complications.

Disease	Target content in exosome	Sample	Method	Scientific mechanism	References
T2DM	Counts of cell-derivedexosomes ↑	Serum	Flow cytometry meta-analysis	1. Total annexin V-positive blood cell microparticles—procoagulant activity could be involved in vascular complications. 2. Endothelial microparticles stimulated by elevated glucose change their molecular composition and increase their biological activity, which may lead to progressive endothelial damage and subsequent cardiovascular complications in diabetes	629–631
Diabetes nephropathy	Counts of cell-derived exosomes ↑	Urinary	Flow cytometry	MiR-26a-5p from adipose-derived mesenchymal stem cell-derived EVs protect against DN	632
	Dipeptidyl peptidase-IV ↑	Urinary	ELISA	The urinary level of microvesicle-bound microvesicle-dipeptidyl peptidase-IV is associated with the severity of diabetic kidney disease	633
	Wilms tumor-1 ↑	Urinary	Western blotting	Among podocyte-derived signal transduction factors in urinary exosomes, WT1 mRNA levels reflected damage of diabetic glomeruli in the patients	634
	AMBP, MLL3 ↑ VDAC1 ↓	Urinary	LC–MS/MS	Comparing DN urine exosomes and healthy controls, it was discovered in a panel of three proteins (AMBP, MLL3, and VDAC1) that they were differentially found in urinary exosomes from DN patients	635
	MiR-130, miR-145, miR-155, miR-424 ↑	Urinary	TaqMan qPCR	High glucose will stimulate mesangial cells and increase the content of miR-145 in mesangial cells and their derived exosomes	636
	Mitochondrial DNA ↓	Urinary	Intrarenal Gene Expression Analysis	Urine exosomes from patients with diabetes and CKD had less mitochondrial DNA, and kidney tissues from patients with diabetic kidney disease had lower gene expression of PGC1a	637
	Elf3 ↑	Urinary	Western blotting	AGE treatment induced the secretion of Elf3-containing exosomes from cultured podocytes, which was dependent on the activation of the TGF-b-Smad3 signaling pathway	638
	MiR-16 ↓	Urinary	RT-qPCR	MiR-16 identified as the most stable endogenous reference gene in data set, making it a suitable endogenous reference gene for miRNA studies of urinary exosomes derived from CKD patients	639
	Gelatinase ↓ ceruloplasmin ↑	Urinary	ELISA	Gelatinase (decreased activity) and ceruloplasmin (increased levels), in the urinary exosomes of diabetic kidney patients were in agreement with the alterations of these two proteins in the kidney tissue	640
Diabetic cardiomyocytes	Counts of exosomes ↑	Blood	Flow cytometry	Exosomes from diabetic rats no longer activated the ERK1/2 and HSP27 cardioprotective pathway and were no longer protective in a primary rat cardiomyocyte model of hypoxia and reoxygenation injury. Exosomes from diabetic plasma have lost the ability to protect cardiomyocytes, but protection can be restored with exosomes from nondiabetic plasma	641
	Hsp20 ↓	Serum	LC–MS/MS	Elevation of Hsp20 in cardiomyocytes can offer protection in diabetic hearts through the release of instrumental exosomes	642
	MiR-320 ↑	Serum	TaqMan qPCR	Cardiomyocytes exert an anti-angiogenic function in type 2 diabetic rats through exosomal transfer of miR-320 into endothelial cells	643
	MiR-126 ↓	Serum	TaqMan qPCR	MiR-126 targets insulin receptor substrate (IRS)-1 expression via PI3K/Akt signaling pathways suggests that it is involved in IR modulation	644
	MiR-7 ↑	Serum	RT-qPCR	MiR-7 was demonstrated to be involved in b-cell dysfunction and insulin secretion	608
Diabetic Charcot neuroarthropathy (CN)	Counts of exosomes ↑	Plasma	Flow cytometry	The concentration of EVs is related to elevation of markers of inflammation (CRP and foot temperature difference) in acute diabetic CN	645
Gestational diabetes	Counts of endothelial cell exosomes ↑	Serum, plasma	Western blotting, RT-qPCR	Exosomal Ang2 secretion is regulated by the PI3K/Akt/eNOS and syndecan-4/syntenin pathways	646,647

Note: Reprinted with permission from Sun et al.[628]

Abbreviations: AGE, advanced glycation end-product; CKD, chronic kidney disease; CRP, C-reactive protein; DM, diabetes mellitus; DN, diabetic nephropathy; EV, extracellular vesicle; LC–MS/MS, liquid chromatography–tandem MS; T2DM, type 2 diabetes mellitus.

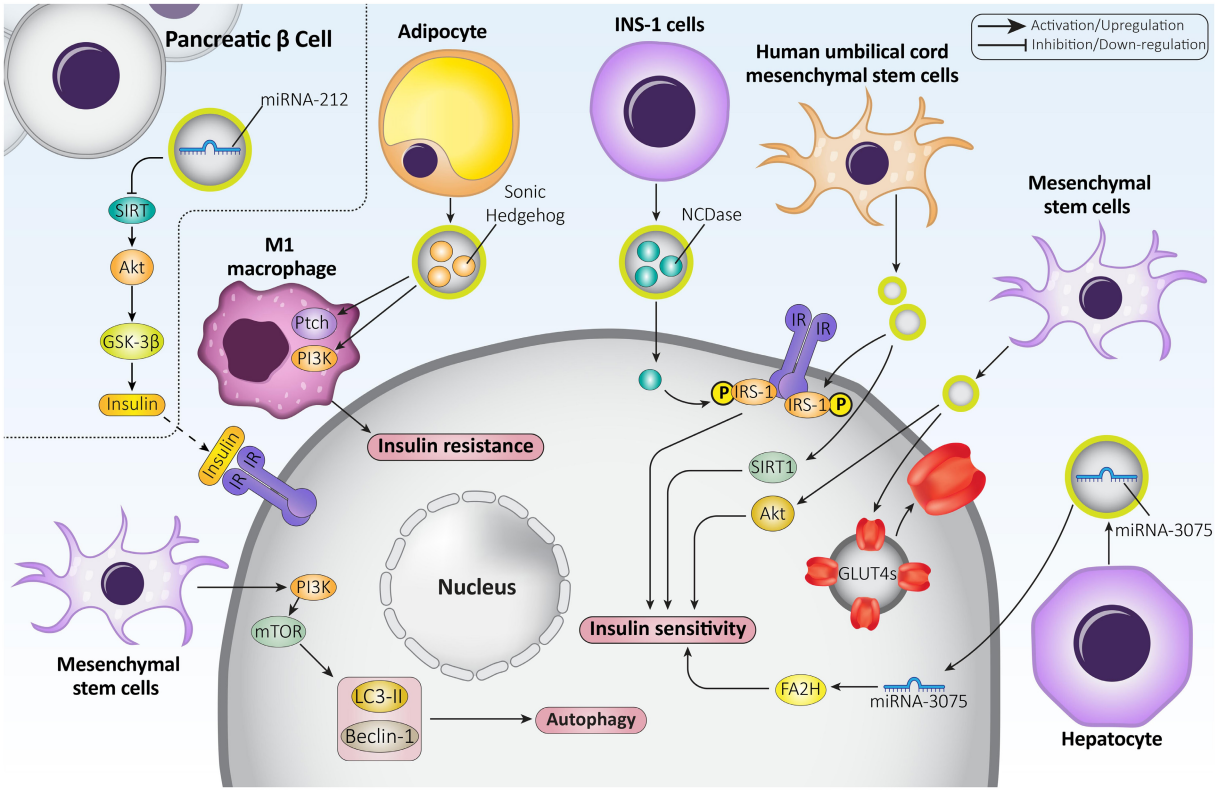

FIGURE 18 Exosomes and insulin resistance/sensitivity in DM. The exosomes demonstrate dual function in DM and can mediate both insulin resistance and sensitivity. For instance, exosomes derived from M1 macrophages can induce insulin resistance and are rich in PI3K and Ptch; on the other hand, exosomes derived from mesenchymal stem cells and hepatocytes induce insulin sensitivity via affecting molecular pathways such as SIRT1 and Akt as well as transferring miRNAs. Reprinted with permission from Ashrafizadeh et al.[665]

the miRNAs' activity. It has been proposed that miRNA-3075 acts as an antidiabetic agent by improving insulin sensitivity which has been shown in hepatocyte-derived exosomes.[663,664] The pro-inflammatory role of macrophages and the progression of insulin resistance are connected (Figure 18, Table 22).

5.1.5 | Exosomes and diabetic wound healing

In diabetic individuals, the healing process of wounds is slowed down, making chronic non-healing wounds much more common.[673] Pro-inflammatory cytokines and proteases are abundant in diabetic wounds, decreasing growth factors in the area.[674–676] Medications for diabetics are administered to about 70% of individuals with the disease. Inflammation, re-epithelialization, collagen deposition, angiogenesis, and proliferation are just a few of the many cellular and molecular processes involved in the intricate process of wound healing.[677,678]

A recent systematic review published by Bailey et al. 2022 titled: "Extracellular Vesicles Derived from MSCs to Treat Diabetes-Related Injuries: A Comprehensive Review and Meta-Analysis of Preclinical Animal Research"[679] discovered numerous benefits of exosomes in the treatment of diabetic wounds. Wound closure was the main result that was assessed, but secondary outcomes demonstrated many advantages including (1) increase in blood vessel density and number, (2) re-epithelialization, (3) collagen deposition, (4) scar width, and (5) inflammation (Figure 19).[679]

5.1.6 | Diabetic-induced neuropathy

Due to focal and widespread nervous system impairments, neuropathy is seen in around 50% of DM patients. Diabetic individuals often have neuropathy, which may cause discomfort and a lower quality of life.[680] In the USA, diabetic neuropathy is the cause of $10 billion in expenses each year.[681] Consequently, actions aimed at managing and avoiding diabetic neuropathy should be taken. Notably, anti-diabetic drugs have shown promise in reducing brain damage caused by DM. Anti-diabetic medications have the ability to greatly reduce neuroinflammation and oxidative damage, hence preventing the onset of neurological disorders like Alzheimer's and Parkinson's diseases. Moreover, antidiabetic medications like GLP-1R and DPP-4i have the potential to enhance the process of neurogenesis and improve cognitive performance.[682]

Exosomes have been shown to possess an ability to lower apoptosis in neurons.[683] Administering paeoniflorin enhances the therapeutic effects of Schwann cell-derived exosomes and supports the stability and integrity of the endoplasmic reticulum. Moreover, the

TABLE 22 Exosomes in regulating insulin resistance, β-cell function, glucose, and lipid metabolism.

Source of exosome	Function	Signaling network	Remarks	References
Hepatocyte	Insulin sensitivity	miRNA-3075/FA2H	The exosomes can deliver miRNA-3075 for decreasing FA2H expression and increasing insulin sensitivity	666
Human umbilical cord mesenchymal stem cells	Insulin sensitivity	SIRT1 IRS-1	Decreasing leptin levels Upregulating expression level of SIRT1 and IRS-1 in mediating insulin sensitivity	662
Mesenchymal stem cells	Insulin sensitivity	IRS-1 Akt GLUT4	Promoting glucose metabolism Increasing phosphorylation of Akt and IRS-1 Elevating membrane translocation of GLUT4	667
INS-1 cells	Insulin sensitivity	IRS-2	NCDase-enriched exosomes promote insulin sensitivity via enhancing IRS-2 phosphorylation Increasing insulin uptake in cells Preventing palmitic acid-induced insulin resistance	661
–	Insulin resistance	TLR4/NF-κB	Silencing SIRT1 induces exosome secretion via autophagy inhibition Exosomes induce insulin resistance via triggering TLR4/NF-κB axis	668
Adipocyte	Insulin resistance	Ptch PI3K	Exosomes possess high levels of Sonic Hedgehog Inducing M1 polarization of macrophages via Ptch and PI3K upregulation	669
Mesenchymal stem cell	β cell protection	miRNA-21/Grp94/apoptosis p38/caspase-3/PARP/apoptosis	The exosomes alleviate ER stress and decrease apoptosis in β cells Exosomes delivering miRNA-21 decrease Grp94 expression to inhibit apoptosis in β cells Exosomes downregulate p38 expression to prevent apoptosis	670
M1 macrophages	β cell dysfunction	miRNA-212-5p/SIRT2/Akt/GSK-3β/β-catenin	The exosomal miRNA-212 reduces SIRT2 expression to inhibit Akt/GSK-3β axis Providing nuclear translocation of β cells Preventing insulin secretion by β cells	671
Mesenchymal stem cell	Glucose and lipid metabolism	AMPK/autophagy	Ameliorating TIIDM via upregulating AMPK expression, promoting Beclin-1 and LC3 levels, resulting in autophagy Autophagy induction enhances lipid and glucose metabolism in cells	672

Note: Reprinted with permission from Ashrafizadeh et al.[665]

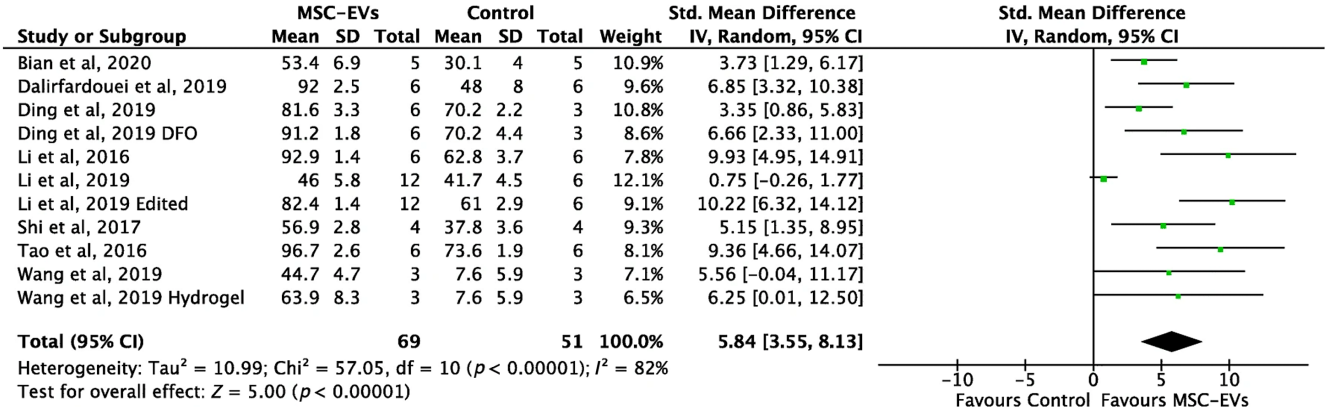

FIGURE 19 Forest plot demonstrating increased wound closure rates of diabetic wounds receiving MSC-EVs. Note the positive impact of exosomes on wound closure in diabetic in vivo models. Reprinted with permission from Bailey et al.[679]

intervention of paeoniflorin enhances the ability of exosomes to inhibit programmed neuron cell death by reducing the expression of GRP78 and IRE1α. These interactions are crucial for the prevention of neuropathy in individuals with diabetes mellitus.[683] There is hope that exosomes produced by MSCs might alleviate diabetic peripheral neuropathy. It has been demonstrated that exosomes with a high concentration of miRNA-146a have the ability to increase the speed at which nerves transmit signals while also potentially reducing the threshold for feeling heat and pressure. To lessen diabetic neuropathy, these exosomes delivered via IV suppress endothelial cell activation and reduce monocyte inflammation. To lessen diabetic neuropathy, the TLR-4/NF-κB axis may be suppressed by miRNA-146a-enriched exosomes.[684]

5.1.7 | Diabetic-induced nephropathy

Another DM consequence that leads to end-stage renal disease is nephropathy.[685] Nephropathy occurs in 25% of patients and develops for a number of reasons. By producing Amadori and advanced glycation end-products, hyperglycemia may lead to diabetic nephropathy. Moreover, the electron transport cycle is triggered by hyperglycemia, which dramatically raises ROS levels and contributes to diabetic nephropathy.[686]

Exosomes may have a therapeutic effect on diabetic kidney disease. MSC-Exos have elevated concentrations of miRNA-125b, which inhibits TRAF6 and triggers Akt signaling. This leads to the activation of autophagy and a reduction in apoptosis, both of which are crucial for mitigating the symptoms of diabetic nephropathy.[687] Autophagy is a crucial biochemical mechanism involved in cell death. In summary, autophagy facilitates the breakdown of aging organelles and macromolecules that are hazardous to primary cell homeostasis. Autophagy has context-dependent roles in both pro-survival and pro-death processes.[682,688–692] Notably, pro-survival autophagy may stop a cell from going through apoptosis.[693] The exosomes produced from MSCs also inhibit mTOR signaling, a negative regulator of autophagy, in order to significantly enhance the levels of Beclin-1 and LC3. These proteins play a crucial role in promoting autophagy and preventing apoptosis helping alleviate diabetic nephropathy.[569]

5.1.8 | Diabetic-induced endothelial dysfunction

Around the globe, gestational diabetes is prevalent in around 5%–20% of pregnancies. Endothelial dysfunction is one of the diseases that arise in gestational diabetes mellitus.[694] Fetal-placental endothelial dysfunction is caused by increased production of nitric oxide (NO) and improved transport of L-arginine.[695,696] While experiments are still in their infancy, exosomes lower the levels of a number of substances during disease progression, including IL-8, MDA, SOD, and—more importantly—ICAM-1, which helps avoid endothelial failure.[697]

5.1.9 | Diabetic-induced erectile dysfunction

One known risk factor for erectile dysfunction is diabetes mellitus which affects 19%–90% of individuals and may manifest up to 10 years before the onset of diabetes mellitus, lowering a man's quality of life and self-esteem.[698–700] In addition to diabetes mellitus, additional risk factors for the development of erectile dysfunction include smoking, cardiovascular illnesses, dyslipidemia, hypertension, and obesity.[701] Vasculogenic variables that mediate arterial inflow or venous outflow problems are the most prevalent causes of erectile dysfunction.[702]

ADSC-Exos have been injected intravenously to increase smooth muscle level relative to collagen and increase intracavernous pressure, as shown by CD31 overexpression.[703] In addition, exosomes reduce the degree of caspase-3 production while simultaneously enhancing the expression of Bcl-2 to inhibit apoptosis. Exosomes obtained from ADSCs have been shown to be effective therapeutic agents for relieving erectile dysfunction in individuals with diabetes mellitus.[703] Exosomes generated from adipose stem cells have the ability to promote angiogenesis and speed endothelial cell

proliferation in the treatment of erectile dysfunction. Moreover, these exosomes decreased fibrosis in the corpus cavernosum.

Further research showed that large quantities of pro-angiogenic factors miRNA-126, -130a, and -132, as well as antifibrotic factors miRNA-let7b and -let7c, were present in exosomes produced from adipose stem cells.[317] According to the trials, the best way to treat erectile dysfunction brought on by diabetes is to avoid fibrosis. Smooth muscle cell exosomes increase the amount of smooth muscle and reduce the buildup of collagen to have an antifibrotic effect. In order to improve erectile dysfunction in diabetics, exosomes upregulate the expression levels of eNOS and nNOS to trigger the NO/cGMP axis.[704]

5.1.10 | Diabetic-induced cardiovascular diseases

Diabetes is also greatly linked to a number of cardiovascular disorders including atherosclerosis, which was previously discussed.[705,706] By inhibiting TGF-β signaling, the exosomes derived from MSCs may lower the expression level of Smad2, therefore improving cardiac fibrosis in diabetic patients.[707] These studies suggest that exosomes may prevent cardiac damage and help avoid DM-mediated heart damage.

5.1.11 | Diabetic-induced eye disorders

The protective effect of exosomes on the retina seems to depend on the route in which they are administered.[708] Exosomes administered subconjunctivally provide superior outcomes than those administered intravenously and arrange the retina's cellular constituents in a well-organized fashion. The optimal method is thought to be intraocular delivery, which enhances retinal layers that resemble the natural retina. Hyperglycemia has been shown to decrease miRNA-222 expression. To slow down retinal damage in diabetic macular degeneration, MSC-Exos increase the expression of miRNA-222.[708]

5.1.12 | Summary of diabetic-induced complications

Diabetes affects millions of individuals worldwide, and the associated complications caused by diabetes are both numerous and difficult to treat. These studies show that a range of diabetic problems arise such as ocular disorders, cardiovascular illnesses, delayed wound healing, erectile dysfunction, endothelial dysfunction, and neuropathy which may be ameliorated by exosomes. Table 23 summarizes the use of MSC-Exos for the treatment of many diabetic-related complications.[709] Figure 20 highlights all the benefits related to the use of exosomes for the treatment of diabetes.

5.2 | Hematology disorders

Hematology disorders are often degenerative by nature and can lead to serious complications and life-threatening conditions. MSC-Exos have the ability to transport intricate loads and maintain balance within altered homeostasis, hence regulating diseases or malignancies. Recently, the use of MSC-Exos has had significant impacts on many hematological conditions such as graft-versus-host disease (GVHD),[740] multiple myeloma,[741] acute myeloid leukemia (AML),[742] chronic myeloid leukemia (CML),[743] chronic lymphocytic leukemia (CLL),[744] lymphomas,[745] and myelodysplastic syndrome (MDS).[746] An excellent article by Shen and Chen 2021[747] focused exclusively on the role of exosomes for hematology disorders and highlighted many studies in Table 24 and a summary of all related benefits found in Figure 21.

5.3 | Musculoskeletal degeneration

There are major obstacles to treating musculoskeletal degeneration injuries such as fracture nonunion, muscle fibrosis, reinnervation, compartment syndrome, and infection and inflammation. In the realm of musculoskeletal regeneration, there has been a recent focus on exosomes. Various cell types release these vesicles, which are crucial for cell communication since they transport functional signaling molecules including proteins and RNAs. A multitude of these cargo molecules may be used for reparative functions in skeletal illnesses such as osteoporosis, osteogenesis imperfecta, sarcopenia, and fracture healing. A research conducted by Youssef El Baradie and colleagues in 2021[762] titled "Therapeutic application of extracellular vesicles for musculoskeletal repair and regeneration" comprehensively investigated the many uses of exosomes in both repairing and regenerating musculoskeletal tissues.

5.4 | Osteoradionecrosis and radiation therapy

In a study titled: "An indispensable tool: Exosomes are involved in the treatment of radiation-induced damage," Li and colleagues investigated the numerous benefits of exosomes following radiation therapy.[763] Approximately 70% of individuals with tumors receive radiation at various time intervals.[764] Radiotherapy may improve the rate of tumor control and the quality of life for patients. However, normal tissues often experience radiation-induced damage resulting from radiotherapy. Recent research has shown that exosomes have the potential to serve as biomarkers for many illnesses and have a therapeutic role in radiation-induced damage. They further possess the ability to control the inflammatory response, amplify the regenerative impact on injured tissue, and facilitate the restoration of damaged tissues and cells, hence prolonging their lifespan.

Various degrees of radiation damage reduction may be achieved by using MSC-Exos, which include inherent benefits such as minimal immunogenicity, facile culture separation, potent immunosuppressive properties, robust regenerative capabilities, and versatile multidifferentiation capacities.[765–770] Recently, there has been significant research on MSCs as they pertain to radiation damage. A growing body of data suggests that the therapeutic benefits of MSC therapy

TABLE 23 MSC-Exos used in the treatment of DM complication.

DM complication	MSC types	Effect/involved non-coding RNA	References
Diabetes wound	Bone marrow MSC	Vascularization	710
	Adipose-derived MSC	Vascularization	711
	Adipose-derived MSC	Vascularization/miR-21-5p	712
	Bone marrow MSC	Vascularization	713
	Bone marrow MSC	Regulate inflammation/lncRNA H19	714
	Adipose-derived MSC	Vascularization	715
	Synovium MSC	Vascularization/miR-126-3p	716
	Urine MSC	Vascularization	717
	Adipose-derived MSC	Vascularization and regulate inflammation	718
	Induced pluripotent stem cell	Vascularization	719
	Menstrual blood-derived MSC	Vascularization and regulate inflammation	720
	Adipose-derived MSC	Vascularization	721
	Adipose-derived MSC	Vascularization	722
	Adipose-derived MSC	Vascularization/mmu_circ_0000250	723
	Bone marrow MSC	Vascularization and regulate inflammation	724
	Bone marrow MSC	Vascularization/miR-221-3p	725
	Umbilical cord MSC	Vascularization	726
Diabetic nephropathy	Adipose-derived MSC	Podocyte repair/miRNA-215-5p	727
	Urine MSC	Podocyte repair	728
	Bone marrow MSC	Anti-fibrosis and promote renal function recovery	572
	Bone marrow MSC	Anti-fibrosis and promote renal function recovery	569
	Adipose-derived MSC	Podocyte repair/miR-486	729
	Urine MSC	Podocyte repair/miR-16-5	730
	Umbilical cord MSC	Reduce kidney inflammation and improve kidney function	731
	Umbilical cord MSC	Reduce kidney inflammation and improve kidney function	732
Diabetic retinopathy	Adipose-derived MSC	Retinal repair/miR-222	708
	Umbilical cord MSC	Retinal repair and regulation of inflammation/miR-126	141
Erectile dysfunction	Adipose-derived MSC	Vascularization and anti-apoptosis	703
	Adipose-derived MSC	Promote angiogenesis and anti-fibrosis/miR-126, miR-130a, miR-132, miR-let7b, miR-let7c	317
	Adipose-derived MSC	Vascularization and anti-inflammatory	733
	Bone marrow MSC	Vascularization and anti-inflammatory/miR-21-5p	734
Cognitive dysfunction	Bone marrow MSC	Nerve repair	735
	Bone marrow MSC	Nerve repair and anti-inflammatory/miR-146a	736
	Bone marrow MSC	Nerve repair	280
Diabetic stroke	Bone marrow MSC	Nerve repair/miR-9	737
	Bone marrow MSC	Nerve repair/miR-145	738
Submandibular gland dysfunction	Bone marrow MSC	Salivary gland function repair	739
Diabetic cardiomyopathy	MSC	Reduce myocardial injury and fibrosis	707

Note: Reprinted with permission from Xiong et al.[709]

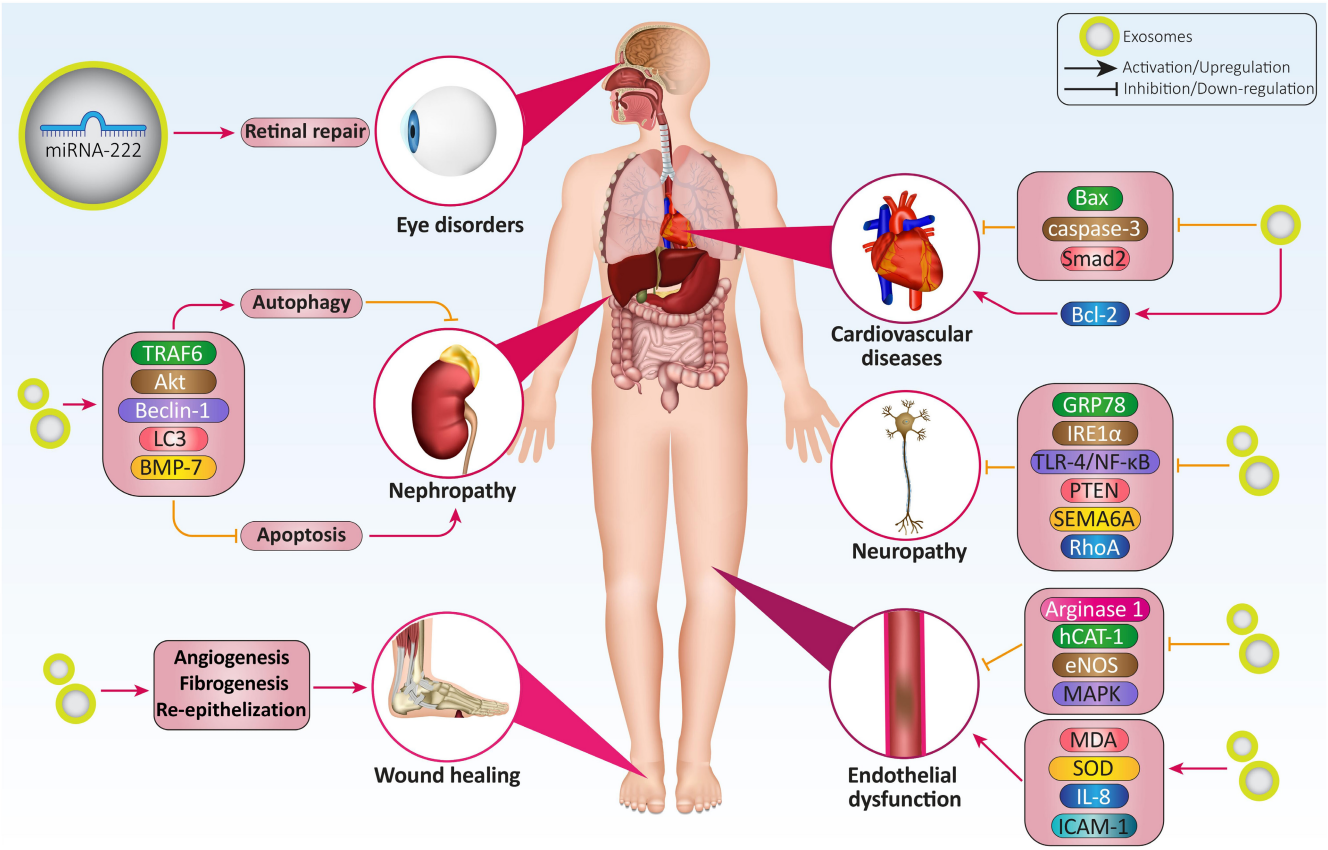

FIGURE 20 Exosomes and diabetic complications. The various kinds of diabetic complications, including eye disorders, cardiovascular diseases, nephropathy, neuropathy, delayed wound healing, and endothelial dysfunction, can be ameliorated by exosomes. Neuropathy and nephropathy are the most common diabetic complications. Apoptosis, autophagy, angiogenesis, and fibrogenesis are among the most common molecular mechanisms affected by exosomes in alleviating diabetic complications. Reprinted with permission from Ashrafizadeh et al.[665]

are mostly attributed to the vesicles released via their paracrine pathways, particularly the actions of exosomes.[771] In the article proposed by Li et al.,[763] exosomes were shown to play a role following radiation on (1) lungs, (2) skin, (3) intestinal, (4) testicular, (5) bone, and (6) hemopoietic system (Figure 22, Table 25). A recent study titled: "The therapeutic potential of exosomes derived from mesenchymal stem cells in the treatment of osteoradionecrosis." further highlighted the potential for exosomes to improve necrotic tissues caused by osteoradionecrosis.[772] While this field is still in its infancy and protocols remain to be developed, there is great therapeutic potential for utilizing exosomes to treat radiation damage.

5.5 | Respiratory diseases

Recent interest has focused on the ability for MSC-EVs to treat chronic respiratory diseases. MSC-EVs have the potential to be a revolutionary cell-free treatment for pulmonary fibrosis, COPD, asthma, and pulmonary arterial hypertension, among other chronic respiratory disorders. The two most common ways to administer MSC-EVs are intravenous and intratracheal. Target cells may receive microRNAs and proteins from MSC-EVs, which further amplifies their therapeutic effects. It is interesting to note that exosomes have been used in several clinical studies for the diagnosis and/or treatment of respiratory disorders and that number is only predicted to rise sharply in the years to come (Figures 23 and 26). Figure 24 summarizes research to date on the topic of exosomes and their associations regarding their regenerative potential.

5.5.1 | Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic lung illness marked by recurrent airway inflammation and permanent, progressive airflow restriction. It significantly impairs the patient's ability to breathe and significantly impacts their daily activities and ability to work.[806,807] The pathophysiology of COPD is approached from a variety of angles, including protease/antiprotease, oxidative stress, epigenetics, cell aging, apoptosis, chronic inflammation, and linear green body function.[808] Genetic mutations and environmental variables are involved. The main risk factor for COPD is exposure to cigarette smoke (CS), whether from

TABLE 24 MSC exosomes in hematological diseases.

Disease	MSC sources	Exosomal cargo	Disease model	Biological effect	References
Refractory GVHD	Human BMSCs	NM	Clinical case	Reduced pro-inflammatory cytokine and improved clinical GvHD symptoms	740
aGVHD	Immortalized human embryonic stem cell-derived MSCs	NM	Mouse GVHD mode	Enhanced Treg production, alleviated GVHD symptoms, and increased survival by APC	748
aGVHD	Human BMSCs	miR-125a-3p	Mouse GVHD model	Prolonged the survival of mice with aGVHD and reduced the pathologic damage by suppressing the functional differentiation of T cells from a naive to an effect or phenotype	140
aGVHD	Human UC-MSCs	NM	Mouse GVHD model	Lowered the number of $CD3^+CD8^+$ T cells; reduced levels of IL-2, TNF-α, and IFN-γ; increased the ratio of $CD3^+CD4^+$/$CD3^+CD8^+$ T cells; and rose serum levels of IL-10	749
GVHD	Human UC-MSCs	TGF-β, IFN-γ, IDO, IL-10	In vitro cell experiment	Promoted PBMCs to differentiate into Tregs via TGF-β and IFN-γ	750
cGVHD	Human BMSCs	NM	Mouse chronic GVHD	Blocked Th17 differentiation and improved the Treg phenotype	751
cGVHD	Human UC-MSCs	NM	Mouse chronic GVHD	Prevented skin fibrosis in the cGVHD mouse model by suppressing the activation of macrophages and B cell immune response	313
MM/lymphoma/leukemia	Young and elderly healthy donor BMSCs	NM	In vitro cell experiment	Antitumor effect existed in the supernatant and not in exosomes; the antiangiogenesis effect depends on the age of donors	752
MM	MM-derived BMSCs	miRNA-15a, IL-2, CCL-2, fibronectin	Mouse MM model	MM patient-derived BMSC exosomes promoted MM tumor growth while normal-derived exosomes inhibited the growth of MM cells	753
MM	Human BMSCs and mouse BMSCs	MCP-1, IP-10, SDF-1	In vitro and in vivo MM model	Favored MM cell proliferation, migration, and survival and induced drug resistance to bortezomib	754
MM	Normal donors and MM BMSCs	NM	In vitro cell experiment	Decreased cells viability, proliferation, migration, and translation initiation with exosomes from normal donor BMSCs, whereas MM MSC exosomes increased	755
MM	Old and young MM-derived BMSCs	miR-340	In vivo model of hypoxic BM in MM	Inhibited MM-induced angiogenesis with exosomes from young BMSCs, and miR-340 inhibited angiogenesis in endothelial cells	756

(Continues)

TABLE 24 (Continued)

Disease	MSC sources	Exosomal cargo	Disease model	Biological effect	References
MM	MM and normal tissue-derived MSCs	LINC00461	In vitro cell experiment	LINC0046 was highly expressed in MSC exosomes and enhanced MM cell proliferation	757
MM	Bortezomib-resistant or bortezomib-sensitive patient MSCs	lncPSMA3, PSMA3-AS1	U266-luc$^+$ xenograft models	Exosomal lncPSMA3-AS1-mediated resistance to proteasome inhibitors by regulating the stability of PSMA3	758
AML	Human BMSCs	S100A4	In vitro cell experiment	Upregulated S100A4 and driven proliferation, invasion, and chemoresistance of leukemia cells	759
AML	Human BMSCs	TGF-B1, miR-155, miR-375	Clinical sample analysis	Released TGF-B1, miR155, and miR375 to mediate extrinsic chemoresistance within the niche in AML	760
AML	HD or newly diagnosed AML patient BMSCs	miR-26a-5p, miR-101-3p, miR-23b- 5p, miR-339-3p, miR-425-5p	Clinical sample analysis	Identified candidate miRNAs that provide new insights regarding leukemogenesis and new treatment strategies	742
CML	Human UC-MSCs	NM	In vitro cell experiment	Enhanced the sensitivity of K562 cells to imatinib (IM) via activation of the caspase signaling pathway	761
CML	Human BMSCs	miR-15a	CML xenograft tumor model	Inhibited CML cell proliferation, decreased their sensitivity to IM, and promoted IM resistance	743
CLL	Human BMSCs	NM	In vitro cell experiment	Rescued leukemic cells from spontaneous or drug-induced apoptosis, enhanced their migration, and induced gene expression modifications	744
Hodgkin lymphoma	MSC cell lines	ADAM10	In vitro cell experiment	Induced release of cytokines, like TNFα, sCD30, or CD30 shedding by HL cells	745
MDS	HD and MDS patient BMSCs	miR-10a, miR-15a	In vitro cell experiment	MDS BMSC-derived cargoes overexpressed miR-10a and miR-15a and enhanced cell viability and clonogenic capacity of CD34$^+$ cells	746

Note: Reprinted with permission from Shen and Chen.[747]

Abbreviations: aGVHD, acute GVHD; HD, health donor; IM, imatinib; IP-10, interferon-inducible protein 10; MCP-1, monocyte chemoattractant protein 1; MDS, myelodysplastic syndrome; miRNAs, microRNAs; NM, not mentioned; SDF-1, stromal cell-derived factor 1; UC-MSC, umbilical cord MSC.

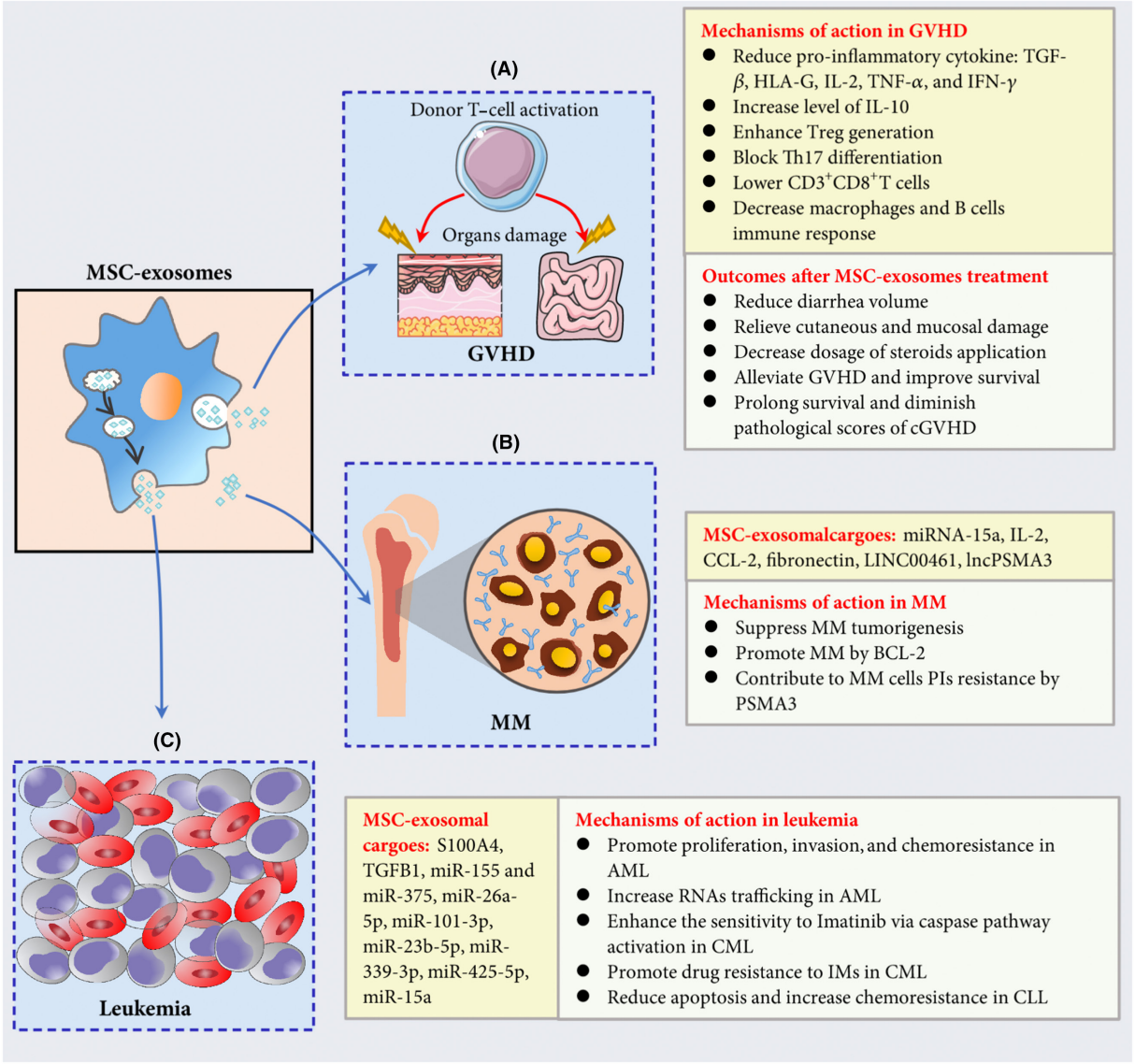

FIGURE 21 Schematic diagram of molecular mechanisms MSC exosomes in hematological diseases. (A) The action of MSC exosomes and subsequent clinical outcomes in GVHD. (B) A brief outline of exosomal cargoes and underlying mechanisms of MSC exosomes in MM. (C) Exosomal loadings and potential effects of MSC exosomes in the diseases of AML, CML, and CLL. AML, acute myeloid leukemia; cGVHD, chronic GVHD; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HLA-G, human leukocyte antigen-G; IM, imatinib; MM, multiple myeloma; PIs, proteasome inhibitors. Reprinted with permission from Shen and Chen.[747]

secondhand smoke or active smoking.[809,810] In some developing nations, exposure to chemicals at work and environmental pollution are major causes of COPD.[811] Indoor air pollution exposure is linked to chronic obstructive pulmonary disease and may even have an impact on fetuses. The World Health Organization (WHO) lists COPD as the third most common cause of mortality worldwide. According to statistical forecasts, the number of fatalities from chronic obstructive pulmonary disease will reach 4.4 million by 2040, with low-income and middle-income nations accounting for 90% of these deaths.[812] Issues related to the airway epithelium, such as initial contact and prolonged exposure to CS, can cause epithelial cells to produce pro-inflammatory medium, senescence-associated secretory phenotype (MCP-1, IL-1, IL-6, and IL-8), and damage-associated molecular patterns (HIG box, heat shock proteins, receptor for advanced glycation end products). The contents that are released into systemic and pulmonary circulation[813,814] may accelerate the development of COPD by causing damage to the alveoli and lung tissue.[815] The degeneration of lung structure and function cannot be reversed by current COPD therapy approaches; they can only slow down the loss of lung function. Consequently, it is critical to comprehend the molecular process behind the onset and progression of COPD for the purpose of improving the therapeutic treatment plan.

Currently, the primary pharmaceuticals used for COPD treatment are bronchodilators, which are derived from treatments of asthma. However, in COPD patients, the addition of inhalation corticosteroids (ICSs) is associated with a reduced risk of exacerbation and mortality. Nevertheless, the majority of patients do not exhibit

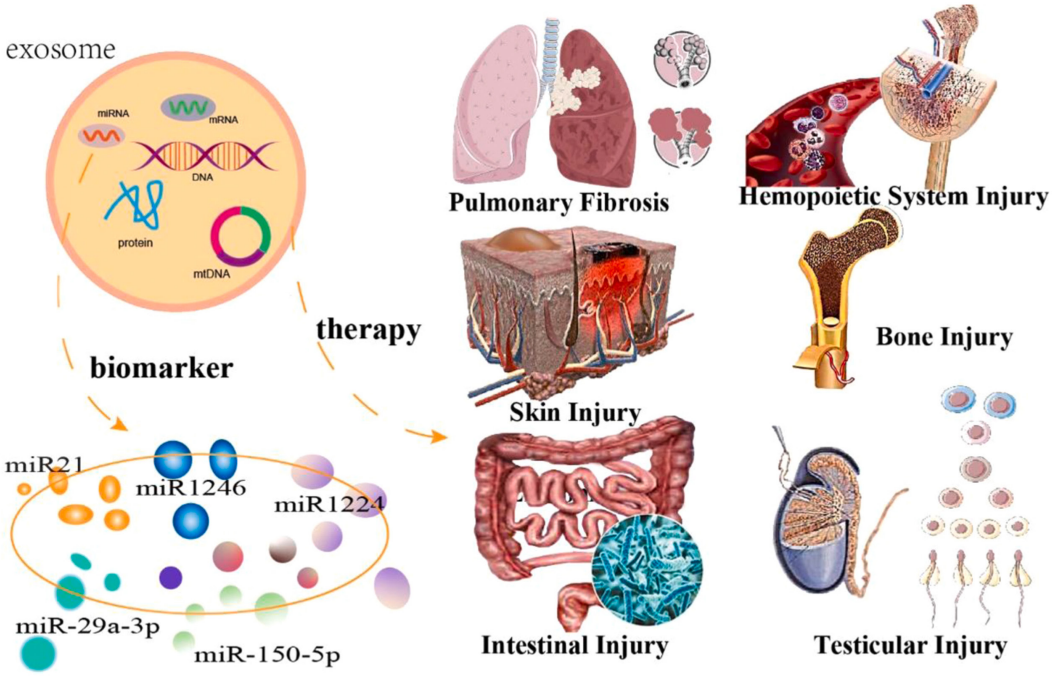

FIGURE 22 Exosomes as an indispensable tool play a role in biomarker and therapy for radiation damage. Exosomes carry many proteins and nucleic acids, which become potential biomarkers for a variety of diseases. And they show broad prospect in the treatment of radiation-induced lung injury, skin injury, intestinal injury, bone injury, testicular injury, and hemopoietic system injury. Reprinted with permission from Li et al.[763]

TABLE 25 Clinical studies of exosomes affiliated with improvements post-radiation therapy.

Source	miRNAs/proteins	Signaling pathway	Function	References
Lung	miR-28-5p	PI3K/Akt	Regulates MSCs ability	773
Pulmonary epithelial cells	Caspase-3	ROCK I	Reduce lung injury	774
MSCs	KGF	Hippo-Yap	Protecting lung Prevent bone loss	775,776 777
ADSCs			Reduce lung injury Promote wound healing	778 779–783
huc-MSCs	miR-21, miR-221, etc.	β2/SMAD2 Wnt/β-catenin	Inhibit pulmonary fibrosis Promote wound healing	784,785 114
Ovarian carcinoma cells	miR-29b	κB	Promote pulmonary fibrosis	786,787
MenSCs		Let-7/LOX1	Reduce lung injury	788
Human fibroblast	miR-21, miR-126, etc.		Promote angiogenesis	789
BM-SPCs			Alleviate chronic enteritis	790,791
BMSCs	miR-29b	Wnt/β-catenin	Reduce radiation enteritis Alleviate osteoporosis Weaken radiation-induced bone loss Reverse radiation-induced bone marrow damage	792 793 794 795
Brest milk			Prevent enterocolitis	796–798
Mice macrophages	G-CSF, MIP-2	TLR4	Remain the function of testis	799
Serum		Hippo, PI3K-Akt	HSCs protection	800–802

Note: Reprinted with permission from Li et al.[763]

Abbreviations: ADSCs, adipose-derived stem cells; BMSCs, bone marrow-derived mesenchymal stem cells; BM-SPCs, bone marrow-derived stromal pro-genitor cells; huc-MSCs, human umbilical cord mesenchymal stem cells; MenSCs, menstrual blood-derived endometrial stem cells; MSCs, mesenchymal stem cells.

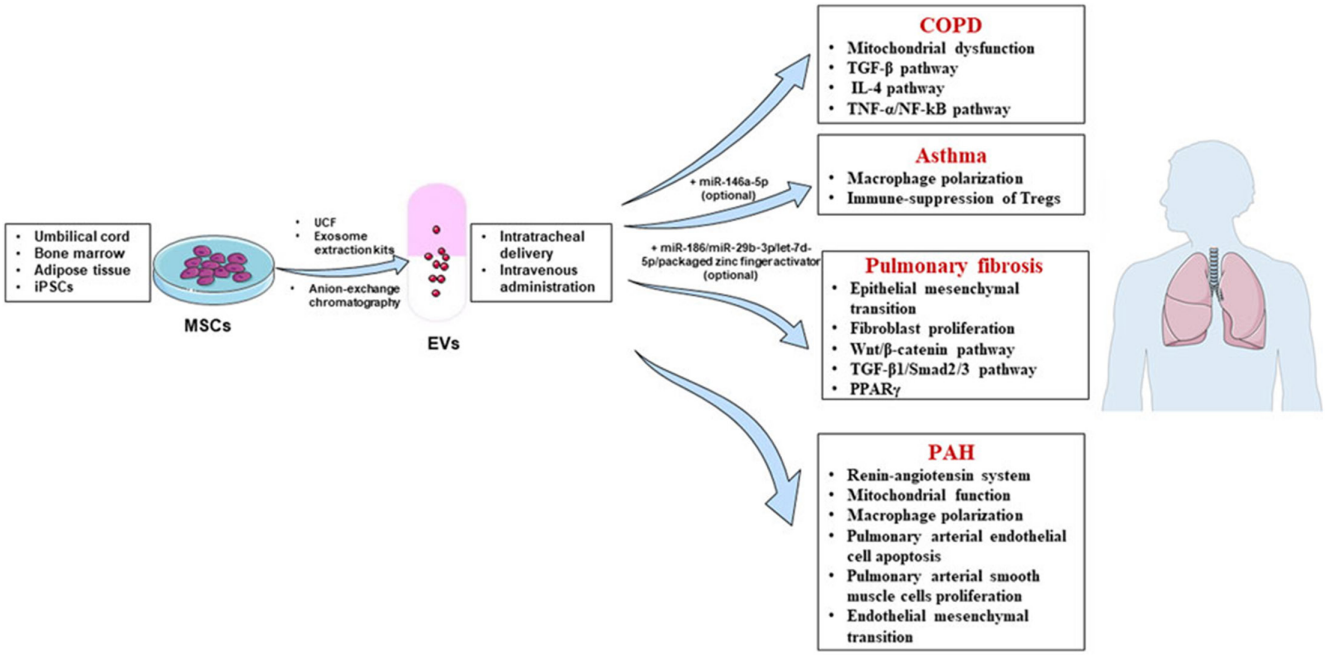

FIGURE 23 Mechanisms of mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) in treating chronic respiratory diseases. Sources of MSC-EVs: umbilical cord, bone marrow, adipose tissue and induced pluripotent stem cells (iPSCs); isolation methods: ultra-centrifugation (UCF), exosome extraction kits and anion-exchange chromatography; treatment routes: intratracheal delivery and intravenous administration; diseases: chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, and pulmonary arterial hypertension (PAH). Reprinted with permission from Ma et al.[803]

sensitivity to steroids, and the administration of high doses amplifies the likelihood of developing pneumonia.[816] Consequently, it is imperative to provide COPD patients with a targeted therapy that addresses their important needs. Additionally, there is a significant need for medications that may prevent the worsening of the illness, as well as the development of pulmonary hypertension and other problems associated with COPD.

In CS-exposed human pulmonary microvascular endothelial cells (HPMECs), Sun et al.[817] observed higher miR-206 expression as well as an increase in caspase-3 and HPMEC apoptosis. MiR-206, Notch3, and VEGFA mRNA levels were negatively correlated. They found that miR-206 targets Notch3 and VEGFA to modulate COPD vascular remodeling.[817] Additionally, anti-miR-27-3p may halt the inflammatory process, reduce BALF inflammatory cytokines, and decrease neutrophil and macrophage infiltration in the lungs. Another study found that overexpressing miR-3202 in COPD may reduce the increase in T lymphocyte IFN-g and TNF-a caused by CSE while increasing Fas and FasL. High miR-3202 levels decrease T-cell apoptosis and protect human bronchial epithelial cells by targeting FAIM 2.[818] Remarkably, 43 papers were included in a recent systematic review on the use of exosomes for COPD by Gomez et al.[819] The investigations were categorized based on the pathophysiological function of EVs, their origin and cargo, their contribution to COPD exacerbations, and their diagnostic value.[819]

5.5.2 | Asthma

Asthma is one of the most common respiratory diseases for which current diagnostic and treatment strategies are still inadequate despite significant advancements.[820–823] The symptoms associated with asthma such as wheezing, shortness of breath, coughing, chest tightness, and recurring signs of varying levels of intensity and severity, are primarily caused by reversible airway blockage resulting from easily induced bronchospasm and increased mucus production.[824–827] Alashkar Alhamwe et al.[828] recently reviewed the use of exosomes for the treatment and management of asthma as highlighted in Table 27.

5.5.3 | Pulmonary hypertension

Multifactorial reasons contribute to the debilitating nature of pulmonary hypertension (PH).[835] Pulmonary vascular resistance is influenced by many etiologies and results in right heart failure. Five types of PH are distinguished based on the hemodynamic characteristics that influence pathogenesis.[836] Based on the global prevalence, nearly 70 million individuals are impacted by PH worldwide.[837,838] Some of the pathologic aspects include dysfunctional endothelial cells (ECs), the proliferation of fibroblasts and smooth muscle cells (SMCs), communication between pericytes, and detrimental changes in ECs and mesenchymal

TABLE 26 Clinical trials in exosomes therapy in respiratory diseases.

No	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
1.	The use of exosomes for the treatment of acute respiratory distress syndrome or novel coronavirus pneumonia caused by COVID-19 (ARDOXSO) Sponsor: AVEM HealthCare	NCT04798716	United States, California	Open label, interventional, mesenchymal stem cell exosomes for the treatment of COVID-19-positive patients with acute respiratory distress syndrome and/or novel coronavirus pneumonia *N*: 55	Measure and report the number of participants with treatment-related adverse events Tabulate and report the number of IMV days for patients receiving ARDOXSO™ perinatal MSC-derived exosome therapy	Not yet recruiting July 21, 2021	Phase 1 Phase 2
2.	Safety and efficiency of method of exosome inhalation in COVID 19-associated pneumonia (COVID-19EXO2) Sponsor: Olga Tyumina	NCT04602442	Russian, Samara	Randomized, interventional, the extended protocol of evaluation of safety and efficiency of method of exosome inhalation in COVID-19 associated two-sided pneumonia *N*: 90	Number of participants with nonserious and serious adverse events during trial Number of participants with nonserious and serious adverse during inhalation procedure	Enrolling by invitation October 26, 2020	Phase 2
3.	Evaluation of safety and efficiency of method of exosome inhalation in SARS-CoV-2 associated pneumonia. (COVID-19EXO) Sponsor: State-Financed Health Facility "Samara Regional Medical Center Dinasty"	NCT04491240	Russian, Samara	Randomized, interventional, the protocol of evaluation of safety and efficiency of method of exosome inhalation in SARS-CoV-2 associated two-sided pneumonia *N*: 30	Number of participants with nonserious and serious adverse events during trial Number of participants with nonserious and serious adverse during inhalation procedure	Completed November 4, 2020	Phase 1 Phase 2
4.	A safety study of IV stem cell-derived extracellular vesicles (UNEX-42) in preterm neonates at high risk for BPD Sponsor: United Therapeutics	NCT03857841	United States, Colorado, Massachusetts, Mississippi, Missouri	Randomized, interventional, a safety study of intravenous infusion of bone marrow mesenchymal stem cell-derived extracellular vesicles (UNEX-42) in preterm neonates at high risk for bronchopulmonary dysplasia *N*: 3	Number of subjects with treatment-emergent adverse events during the post-treatment phase	Terminated October 12, 2021	Phase 1

TABLE 26 (Continued)

No	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
5.	A clinical study of mesenchymal stem cell exosomes nebulizer for the treatment of ARDS Sponsor: Ruijin Hospital	NCT04602104	China, Shanghai	Randomized, double-blinded, controlled clinical study of allogeneic human mesenchymal stem cell exosomes (hMSC-Exos) nebulized inhalation in the treatment of acute respiratory distress syndrome *N*: 169	Incidence of adverse reaction Time to clinical improvement 28-day mortality	Recruiting November 2, 2021	Phase 1 Phase 2
6.	A tolerance clinical study on aerosol inhalation of mesenchymal stem cells exosomes in healthy volunteers Sponsor: Ruijin Hospital	NCT04313647	China, Shanghai	Open label, non-randomized, interventional, a tolerance clinical study on aerosol inhalation of mesenchymal stem cells exosomes in healthy volunteers *N*: 24	Number of participants with adverse reaction (AE) and severe adverse reaction (SAE)	Completed August 4, 2021	Phase 1
7.	Omics sequencing of exosomes in body fluids of patients with acute lung injury Sponsor: Nanfang Hospital of Southern Medical University	NCT05058768	China, Guangdong	Observational, case–control, exosomes in urine, blood, and alveolar lavage fluid from patients with acute respiratory distress syndrome (ADRS) were sequence by omics *N*: 180	Compare the omics differences of blood samples between the experimental and control groups Compare the omics differences of urine samples between the experimental and control groups	Recruiting September 28, 2021	Case–control
8.	Exosomes derived from placental mesenchymal stem cells as treatment for severe COVID-19: Phase 1 and 2 clinical trials Sponsor: Omid Cell and Tissue center	IRCT20200413047063N2	Tehran, Iran	Participants were randomly divided into two equal groups using a randomized double AB blocking method based on a random number table. Patients allocated randomly to two groups: (1) Intervention 1, Patients will receive Six doses of Exosomes. (2) Control, Patients will receive conventional therapy *N*: 50	Adverse events assessment	Recruiting July 8, 2021	Phase 1 Phase 2

(Continues)

TABLE 26 (Continued)

No	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
9.	Molecular profiling of exosomes in tumor-draining vein of early-staged lung cancer (ExOnSite- Pro) Sponsor: University Hospital, Limoges	NCT04939324	France, Limoges	Open label, single group assignment, Analyze du Profil moléculaire Des Exosomes de la Veine Pulmonaire Dans le Cancer Bronchique de Stade précoce *N*: 30	Evaluate size distribution, concentration and molecular profiling of pulmonary vein exosomes at inclusion	Recruiting November 11, 2021	Not applicable
10.	A pilot clinical study on inhalation of mesenchymal stem cells exosomes treating severe novel coronavirus pneumonia Sponsor: Ruijin Hospita	NCT04276987	China, Shanghai	Open label, single group assignment, a pilot clinical study on aerosol inhalation of the exosomes derived from allogenic adipose mesenchymal stem cells in the treatment of severe patients with novel coronavirus pneumonia *N*: 24	Adverse reaction (AE) and severe adverse reaction (SAE) Time to clinical improvement (TTIC)	Completed September 7, 2020	Phase 1
11.	Extracellular vesicle infusion treatment for COVID-19-associated ARDS (EXIT-COVID-19) Sponsor: Direct Biologics, LLC	NCT04493242	United States, Alabama, California, Pennsylvania, Texas	Randomized, double-blinded, bone marrow mesenchymal stem cell-derived extracellular vesicles infusion treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a phase II clinical trial *N*: 120	7 day change in partial pressure of arterial oxygen to fraction of inspired oxygen ratio	Completed December 6, 2021	Phase 2

TABLE 26 (Continued)

No	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
12.	Safety and efficacy of exosomes overexpressing CD24 in two doses for patients with moderate or severe COVID-19 Sponsor: Athens Medical Society	NCT04902183	Greece, Athens, Attica	Randomized, single, a Phase II randomized, single-blind dose study to evaluate the safety and efficacy of exosomes overexpressing CD24 in 10^9 dose versus 10^{10} dose, for the prevention of clinical deterioration in patients with moderate or severe COVID-19 *N*: 90	Collection of serious adverse events Proportion of patients related with respiratory rate and SpO_2 saturation	Recruiting June 15, 2021	Phase 2

Note: Reprinted with permission from Zargar et al.[804]

cells.[839] Medically, these disorders result in blood clot formation, swelling, and constriction of the blood vessels. The major elements that influence pulmonary vascular remodeling are the interactions between cellular instigators such as pulmonary ECs and pulmonary artery SMCs, various immune cells, and molecular recruitment mediators such as cytokines and paracrine products.[840–842] These pathobiological responses worsen the hemodynamic conditions of patients and lead to right heart failure which damages several organs and eventually results in death.[843,844] An increasing amount of evidence indicates that the development of progressive vascular remodeling in PAH is closely associated with pulmonary vascular inflammation brought on by interactions between various immune cells.[845,846]

Exosomes play a crucial role in intercellular signaling and communication throughout the physiological cellular process of vascular remodeling. Apart from the fundamental secretory channels that have been theoretically discovered so far, exosomes, and various additional EVs are novel therapeutic ways to treat pulmonary arterial hypertension.[847] Understanding the traditional channels of secretory proteins that operate on these arteries, as well as the circumstances surrounding the use of nonconventional pathways, are necessary to restore damaged pulmonary vasculature. Exosomes have played a crucial role as immunomodulators in the presentation of antigens and intercellular communication that trigger immune responses. Additionally, new research suggests that exosomes may be important regulators of the inflammatory response, which is one of the processes contributing to the progression of vascular disorders. Despite concerns regarding the excessive proliferative capacity of stem cell treatments, therapies using exosomes provide a robust and promising answer for several illnesses such as PH. One benefit of exosome therapies is their ability to directly be administered at substantial quantities to damaged tissues without risks associated with their native parent MSCs. Table 28 highlights some of these findings.[835]

5.5.4 | Interstitial lung diseases

Interstitial lung diseases (ILDs) are long-lasting pulmonary illnesses that cannot be reversed and have a high impact on both the health and survival of individuals. The diagnostic methods for ILDs are complex and include several factors. Ongoing research has led to significant advancements in the development of effective treatment approaches including EVs which provides a novel approach in the field of diagnostics (biomarkers) and therapy.[857] ILDs may occur idiopathically as a result of exposure to biological, chemical, or small particles, or resulting from co-morbidities such as connective tissue or autoimmune illnesses.[858,859] Chronic, progressive, irreversible fibrosis with substantial morbidity and death is a hallmark of ILDs' natural course.[860–863] If treating the underlying cause of the illness is crucial for managing nonidiopathic ILDs, conventional treatment methods for ILDs include lung transplantation or antifibrotic medication.[864–868] Despite the fact that modern therapies significantly reduce morbidity and death,[869] they do not possess any form of regenerative properties.

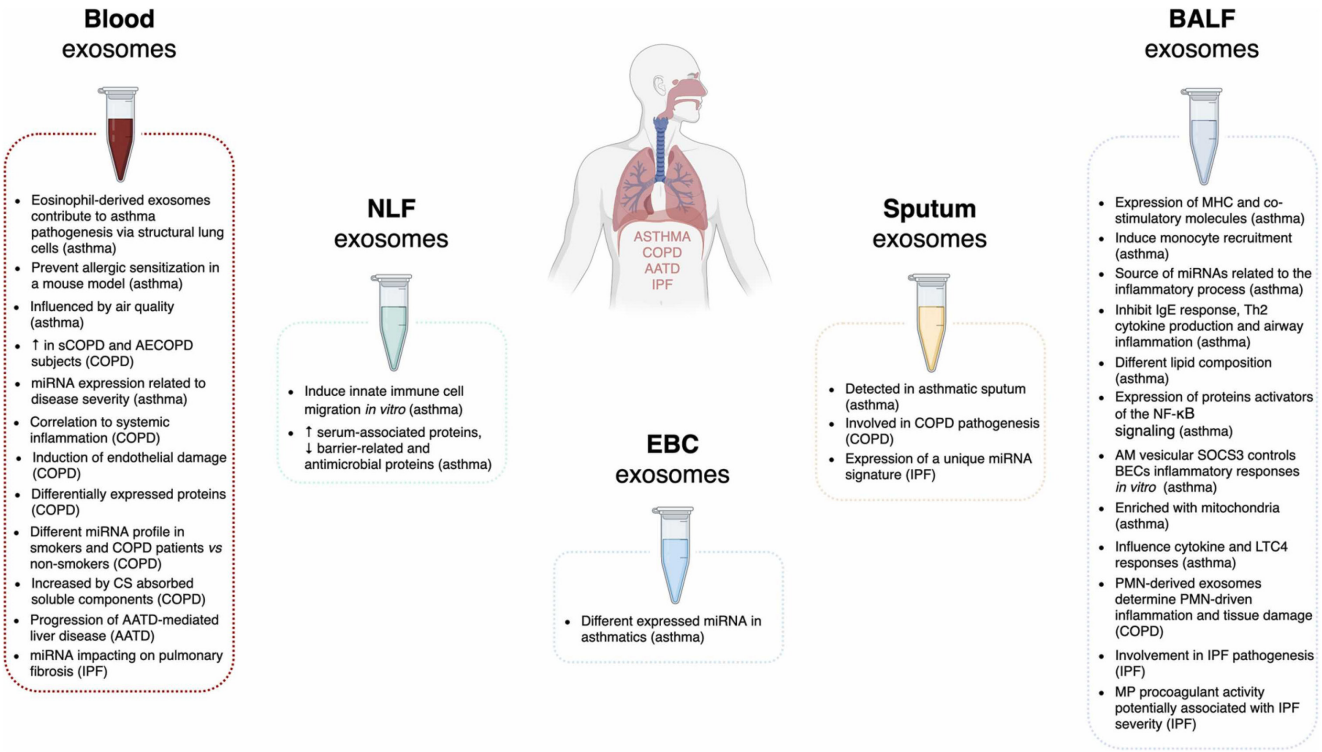

FIGURE 24 Overview of biofluid-derived extracellular vesicles in chronic respiratory disease research. Reprinted with permission from Purghe et al.[805]

TABLE 27 Major asthma-related cellular and systemic effects of extracellular vesicles (EVs) released by mesenchymal stem cells (MSCs).

EVs	Source cells/tissue	Recipient	Main effect(s)	Publication
MVs	Equine amniotic MSC	Horse	Reduction in TNF-α secretion and, to a lesser degree, TGF-β and IL-6 from primary alveolar macrophages	829
Exosomes	Human BM-derived MSCs	Human	Upregulation of IL-10 and TGF-β1 secretion from PBMCs of asthmatics and promotion of proliferation and immunosuppressive capacity of Tregs	830
EVs	Human/mouse BM-derived MSCs	Mouse	Amelioration of *Aspergillus* extract-induced AAI in sensitized animals	831
miR-1470-containing Exosomes	Human MSCs	Human	Promotion of Tregs differentiation from $CD4^+$ T cells isolated from PBMCs of acute asthmatics	142
Exosomes	Mouse adipose Tissue-derived MSCs	Mouse	Effective suppression of the maturation of BM-derived DCs as reflected by decreased IL-6 release but augmented IL-10 and TGF-β secretion	832
EVs	Human adipose Tissue-derived MSCs	Mouse	Reduced symptoms and cellular and molecular features of OVA-induced AAI as well as lung TGF-β levels in OVA-sensitized animals	833
Exosomes	Mouse adipose Tissue-derived MSCs	Mouse	Attenuating effect on airway remodeling in a model of OVA-induced AAI could be further augmented by genetic modifications of MSCs	834

Note: Reprinted with permission from Alashkar Alhamwe et al.[828]

Abbreviations: AAI, allergic airway inflammation; BM, bone marrow; DCs, dendritic cells; IL-10, interleukin-10; MVs, microvesicles; OVA, ovalbumin; PBMCs, peripheral blood mononuclear cells; TGF-β1, transforming growth factor beta 1; Tregs, regulatory T cells.

TABLE 28 Therapeutic role of stem cells-exosome in pulmonary arterial hypertension.

Exosome source	Cargo molecules	Research object	Role	References
Human AdMSCs	PDGF VEGF FGF	Human Microvascular Endothelial cells	• Modulating effect on pro-angiogenic and anti-angiogenic factor	Lopatina et al.[848]
Human AdMSCs	miR-191	MCT rat model Hypoxic rat model	• Ameliorating effect on the MCT-induced PAH pathology via BMPR2 degradation	Zhang et al.[849]
Human MSCs	miR-196b	Sugen5416/hypoxic Rat model	• Preventing and reversing effect on pulmonary artery pressure, right ventricular hypertrophy, and pulmonary vascular remodeling • Modulating effect on macrophage recruitment to the lung, promote the alternative (M2) macrophage activation pathway, and increase vessel formation	Klinger et al.[850]
Human MSCs/mice MSCs	miR-21, 145, 199a	MCT mice model	• Anti-proliferative, apoptotic, or senescent effects on a variety of hyperproliferative cells • Modulating effect on pulmonary vascular remodeling	Aliotta et al.[851]
Mice mesenchymal stromal cell	miR-204	Hypoxic mice model	• Suppression effect on hyper-proliferation by STAT3 mediating signaling	Lee et al.[852]
Human placental MSCs	miR-210	Human placenta microvascular endothelial cells	• Facilitating effect on placental microvascular endothelial cells migration and vascularization	Komaki et al.[853]
Human UC-MSCs	CD63, CD81, TS101, Alix	MCT rat model Hypoxic rat model	• Attenuating effect on PH pulmonary vascular remodel • Reduction effect on excessive proliferation PASMCs by p-GSK3β signaling in PH • Protective effect on vascular remodeling and hypoxic PH • Inhibitory effect on proliferative STAT3 signaling in PAECs	Salomon et al.[854]
Human umbilical cord Wharton's Jelly MSCs	CD34, CD45, CD73, CD90, CD105, HLA-DR	MCT rat model	• Protective effect on PH vascular remodeling by regulating Wmt5a/BMPR2 signaling	Zhang et al.[855]
Human umbilical cord Wharton's Jelly MSCs	ALIX, TSG101, CD81, CD9, CD63, Flotilin-1	Hypoxic mice model	• Restoring effect on lung architecture • Decreasing effect on fibrosis and pulmonary vascular muscularization, ameliorating PH	Willis et al.[856]

Note: Reprinted with permission from Oh et al.[835]

Abbreviations: AdMSC, adipose-derived mesenchymal stem cell; FGF, fibroblast growth factor; MCT, monocrotaline; MSC, mesenchymal stem cell; PAEC, pulmonary arterial endothelial cell; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial smooth muscle cell; PDGF, platelet-derived growth factor; PH, pulmonary hypertension; STAT3, signal transducer and activator of transcription 3; UC-MSC, umbilical cord-derived mesenchymal stem cell; VEGF, vascular endothelial growth factor.

The involvement of EVs in parenchymal lung damage and interstitial fibrosis is a novel and exciting field of study.[870–872] Critical advantages of EVs exist in their mechanistic interventions in the therapy of ILD including reparative, antifibrotic, and immunomodulatory properties.[873] Although therapeutic EV investigations are in their early stage of study for the management of ILD, preclinical findings are promising treatment approaches.[871,874]

According to recent research, BMSC-EVs have been shown to inhibit lung fibrosis and fibroblast proliferation by downregulating the expression of Frizzled Class Receptor 6 (FZD6).[875] While the precise mechanism remains unknown, it was also shown that EVs modulate local pro-inflammatory activation of macrophages and monocytes. Additionally, EVs generated from MSC displayed therapeutic effectiveness in lung fibrosis produced by silica and bleomycin.[876]

6 | REGENERATIVE PROCEDURES

Therapeutic exosomes have been utilized successfully for many years owing to their ability to improve many conditions and diseases

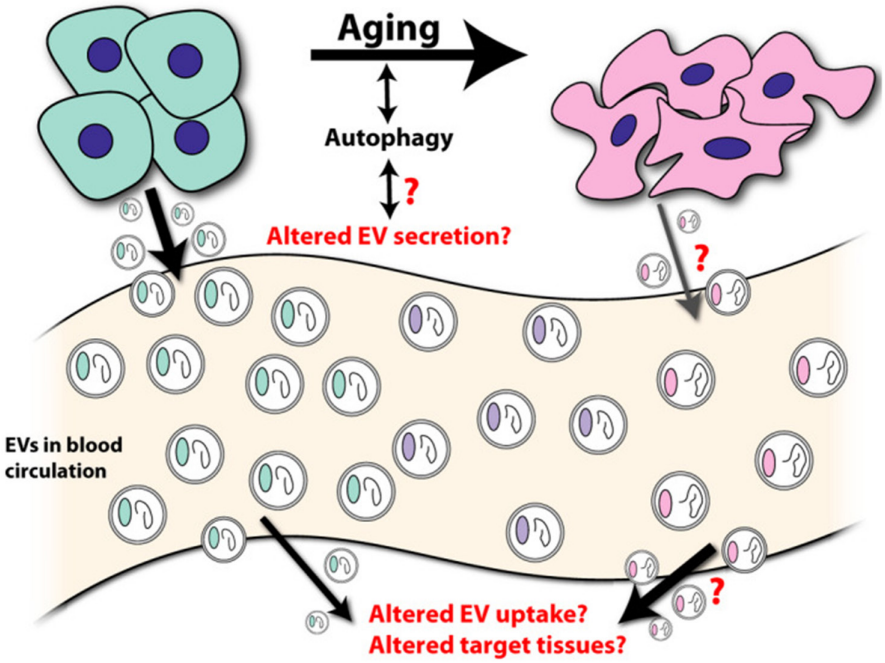

FIGURE 25 Changes to circulating extracellular vesicles (EVs) with age. Together, studies suggest that there may be an age-dependent decrease in the concentration of circulating EVs and concomitant changes to EV protein (colored oval within EVs) and EV nucleic acid (curled line within EVs) with age. It remains unknown whether these changes reflect altered secretion, uptake, or rerouting of EVs with age. Autophagy is an important regulator of aging and shares substantial regulatory overlap with EV biogenesis and degradation, but potential interactions between these relationships have not been thoroughly investigated. Reprinted with permission from Lananna et al.[877]

due to their stability and delivery of signaling molecules in a safer manner. This section focuses more specifically on their ability to improve and regenerate damaged tissues in many fields of medicine. These include bone, cartilage, cutaneous wounds, dermatologic applications, dental, vascular, and spinal tissue regeneration.

6.1 | Antiaging

The use of exosomes has improved various cognitive disorders, including Alzheimer's disease, dementia, and multiple sclerosis, with an ability to cross the blood–brain barrier and help repair functions of various cells and their associated tissues. Owing to these abilities, many clinicians have also utilized exosome therapy as a means to prevent aging and especially cognitive function decline.[877]

Recent research indicates that exosomes control both the pathophysiology of age-related illnesses and systemic aging. Exosome studies have undoubtedly focused on their capacity to preserve human health span. It is interesting to note that the biological usefulness of EVs varies depending on the conditions of the cell/tissue source. Therefore, EVs released by aging or diseased cells may have deleterious effects on receiving cells, while EVs released by young or healthy cells may encourage functional improvement.[877] Therefore, it is important to comprehend the duality of EVs and fully understand that the cell source may shift their positive benefits from an antiaging intervention.[877]

For almost 60 years, there has been credible scientific backing for the once-mythological notion that youthful blood might have antiaging advantages. Even though these early parabiosis trials were fascinating, until much more recently, it was unclear how fresh blood might have rejuvenating benefits.[878] Therefore, it is becoming increasingly clear how extracellular vesicles and exosomes support a variety of biological processes, including aging.[371,878,879] There is already a significant and rapidly expanding body of evidence that confirms the crucial role of EVs in regulating systemic aging and various age-related problems such as inflammation (the chronic inflammation that occurs with advancing age), cellular senescence, metabolic dysfunction, cardiovascular disease, cancer, and neurodegeneration.[371,878,880,881] Moreover, it is possible to utilize age-related alterations in EVs as readily available indicators of aging.[882]

According to recent data, EVs undergo significant alterations as human's age (Figure 25).[877] A comparable decline in the total amount of EVs circulating between young and elderly participants was observed by several research groups.[877,883] As a preventive measure to reduce risks, many patients who suffer from disorders that impair cognitive function may receive exosomes by IV, much as in the case of Parkinson's disease, multiple sclerosis, etc. These exosomes must be made from suitable sources and specifically targeted at immune function (immunosomes) in order to enhance functional recovery with the correct signaling molecules.

6.1.1 | Blood-based antiaging therapies

Numerous research studies have demonstrated that blood-based therapy might help with deficiencies associated with aging. Heterochronic parabiosis, for example, has linked the circulatory systems of young and elderly mouse pairs, revealing a number of substances in young blood that prevent aging phenotypes and in old blood that promote aging.[884–886] By stimulating satellite cells, exposure to a youthful circulatory system revitalizes the ability of muscles to regenerate and returns the proliferative ability of hepatic progenitors.[887] Additionally, neurogenesis and related learning and

memory abilities are impacted by heterochronic parabiosis, which enhances these capabilities in elderly mice.[884–886]

Studies have shown that, in addition to parabiosis, animal plasma obtained from exercise provides antiaging cognitive advantages,[886] suggesting that the plasma EV pool undergoes significant alterations including an increase in EVs when humans exercise.[888] Together, these results indicate that EVs may play a role in the advantages of blood-based treatments to preserve normal physiological processes as people age. A recent exploratory clinical experiment (ClinicalTrials.gov) confirmed the favorable safety and tolerability of using young human plasma to treat individuals with Alzheimer's disease (NCT02256306).[889] More thorough research is necessary to determine how much EVs may mediate the advantages and disadvantages of heterochronic parabiosis or other blood-based treatments.

6.1.2 | Effects of EVs on health span and lifespan

EVs may have a significant role in directly regulating a mammal's longevity and health. Research demonstrates that the hypothalamus is the aging control center.[890–892] Age-related deficits in movement, motor coordination, social interaction, and memory may be lessened by supplementing with EVs generated from hypothalamic neural stem cells.[890]

Another recent study showed that adipose tissue secretes extracellular nicotinamide phosphoribosyltransferase (eNAMPT), a crucial enzyme for NAD+ biosynthesis in animals, into the bloodstream in the form of EVs.[893] In humans and mice alike, the amount of EV-contained eNAMPT in plasma declines with age and, surprisingly in mice, is a good indicator of life expectancy. Activity levels and sleep fragmentation were two of the age-related deficiencies that were ameliorated by adipose tissue-specific overexpression of NAMPT, which also prevented the age-related drop in eNAMPT levels and increased median lifespan by 13.4%. 20-month-old rats also showed improvements in insulin secretion, glucose tolerance, memory, and ocular function.[893]

Interestingly, at the conclusion of their study, female mice receiving weekly intraperitoneal injections of EVs carrying eNAMPT which were isolated from young mouse plasma had a longer median and maximum lifespan increase by 10.5% and 16.3%, respectively.[894] In addition, the administration of EVs resulted in the rejuvenation of both physical appearance and activity levels.[894] The hypothalamus is one of the main destinations for EVs carrying eNAMPT released from adipose tissue. Simple NAD infusions have become increasingly popular in standard IV clinics since it is now recognized that a systemic decrease in NAD+ availability is a major cause of systemic aging.[895] Exosomes' capacity to have positive effects on NAD levels has several benefits for lifespan.

Investigating how exosomes affect longevity and health also has enormous potential for cancer prevention. This subject has been intensively studied in various review articles.[371,881,896] However; it should be mentioned that EVs may supply elements that favorably reinforce the relevant disease state in the context of aging, senescence, cancer, or other pathologies in addition to having the ability to significantly rejuvenate target tissues. This paradox may best be shown by research examining how EVs produced from BMSCs affects the course of multiple myeloma.[753] Tumor development in vivo was prevented by EVs obtained from normal BMSCs but encouraged by EVs derived from multiple myeloma BMSCs. This impact may have been mediated by changes in EV composition in MM, such as the enrichment of inflammatory molecules like IL6 and the reduction in tumor-suppressive miR-15a.[753]

6.1.3 | EVs and "Inflammaging"

EVs are well recognized for their significant roles in both immune system activation and inhibition.[897,898] It is true that EVs released by cancerous or senescent cells cause telomere degradation and inflammation.[899] Research has shown that the presence of irradiated cancer cells in cell culture medium resulted in a reduction of both telomere length and telomerase activity in the breast cancer epithelial cells that received them.[900] Remarkably, the introduction of EVs produced from youthful fibroblasts resulted in a decrease in cellular aging indicators, such as senescence markers, oxidative stress, lipid peroxidation, and inflammatory factors, in several organs of aged animals.[901] A summary of all related benefits to Immunosome infusions is found in Figure 26.

6.2 | Bone regeneration

The skeletal system primarily comprises bone and cartilage, which are composed of many cellular and molecular constituents. The interplay and synchronization of these cellular and molecular components is crucial for preserving homeostasis and effectively rejuvenating bone and cartilage.[902,903] Health issues related to the musculoskeletal system, mostly caused by osteoporosis, tumors, and fractures, have been more prevalent in recent years.[904]

Many cell types found in bone engage in bidirectional or multidirectional communication with each other (Figure 27). Exosomes have a significant role in the intricate network of cell communication due to their ability to modulate the immune system. Apart from their functions in osteogenic differentiation and bone formation, bone damage often results in the disturbance of nearby blood vessels, which may hinder the successive phases of bone regeneration.[905] Through the production of pro-angiogenic substances, MSCs interact with endothelial cells, promoting angiogenesis.[906]

Based on the results of early clinical trials, MSCs have historically been the most promising cell group (from autologous sources) to use in treating disorders affecting the bones and joints. MSCs may be extracted from a variety of tissues, including bone marrow, adipose tissue, and oral tissues including gingiva, periodontal ligament, and tooth pulp.[907–909] MSCs, in particular, aid in tissue healing because of their capacity to migrate into damaged tissues and owing to their trophic and immunomodulatory

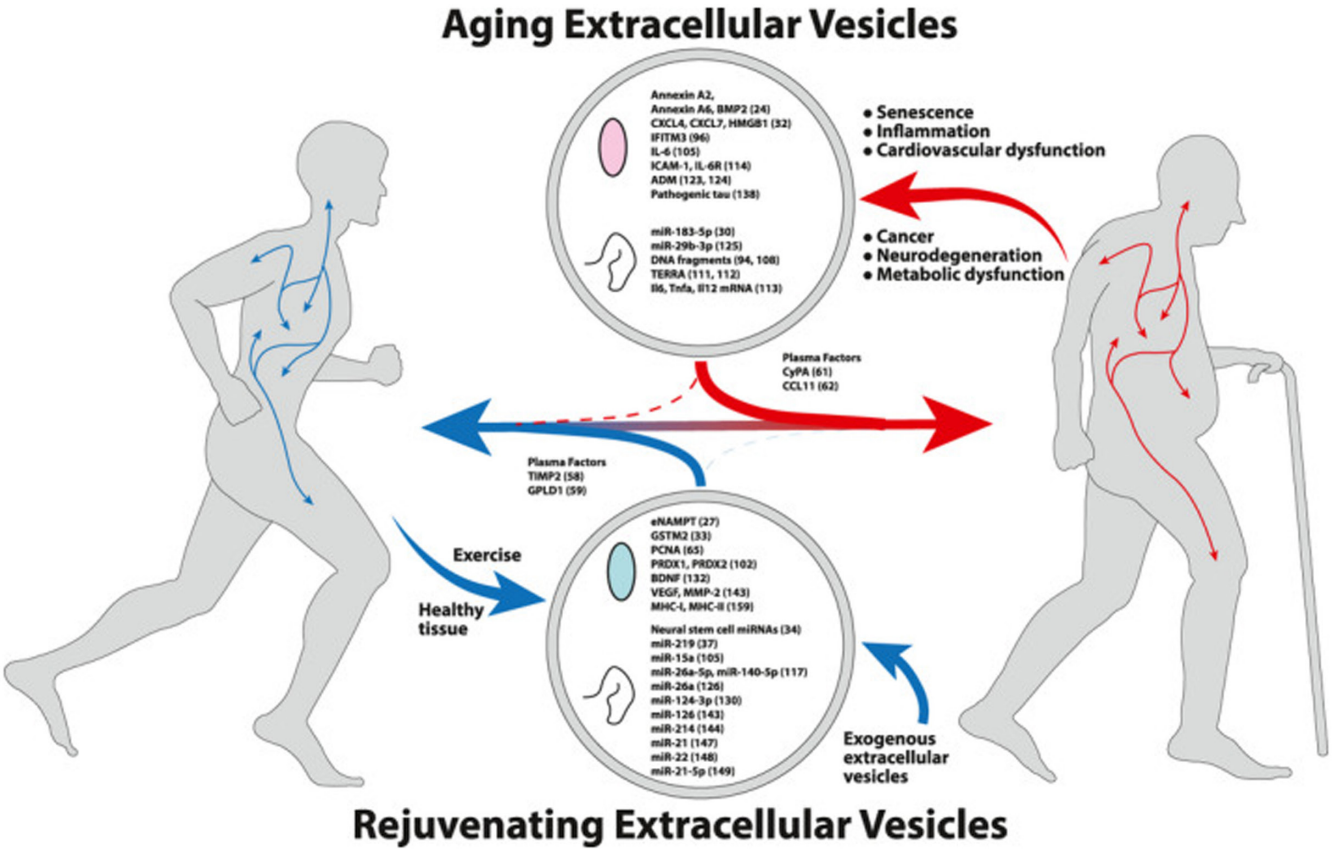

FIGURE 26 Extracellular vesicle theory of aging. Early in life, extracellular vesicles (EVs) serve as beneficial signaling molecules and promote tissue health. As senescent/damaged cells accumulate over the lifespan of an organism, these cells secrete EVs carrying detrimental cargo. These aging-promoting EVs circulate throughout the body, positively reinforcing aging-related tissue deterioration. At the same time, as an organism ages, the number of rejuvenating or supportive EVs decreases. Beneficial effects seen with EV treatments may then reflect a shift of this balance toward rejuvenating EVs and may be one strategy for circumventing age-related deterioration. Proteins are denoted by colored ovals and nucleic acids are denoted by curled lines. Examples of potential effector molecules found to have detrimental effects (top, aging) or beneficial effects (bottom, rejuvenating) are depicted along with supporting citation. Reprinted with permission from Lananna et al.[877]

effects.[910,911] Additionally, MSCs have the capability for self-renewal and the ability to differentiate into osteoblasts, adipocytes, and chondroblasts in vitro. These characteristics allow them to be increased to therapeutic numbers for many possible applications.[912,913] However, regulatory concerns have restricted effectiveness of MSCs, even from autologous sources.[914,915] Over the past decade, clinical researchers have instead concentrated their efforts on the utilization of exosomes produced from MSCs for bone regeneration.[794,916,917]

The processes of bone regeneration and resorption depend on interactions with the ECM and paracrine signaling between cells. Mechanical stimuli, as well as local and systemic hormonal modulation, impact the network of cells. According to recent research, osteocyte mechanical stimulation results in the Ca^{2+}-dependent release of EVs, including the bone-regulating proteins RANKL, OPG, and sclerostin.[918] This finding suggests that the osteocyte's ability to coordinate tissue-level bone adaptation and control bone metabolism in response to mechanical stimuli is derived by EV release and regulation of RANKL, OPG, and sclerostin secretion.[918]

For the purpose of tissue regeneration, MSC-EVs have been studied on a wide variety of cell types found in bone. MSC-EVs have been shown to improve bone fracture,[919–921] bone defect healing,[916,922–927] facilitate repair in osteogenesis imperfecta,[928] and have been studied in femoral head avascular necrosis brought on by steroids,[929] osteochondral abnormalities,[226,930,931] osteoarthritis (OA),[210,233,238,240] and periodontal disease.[932,933] An overview of the current knowledge between interactions among several cell types involved in bone and cartilage regeneration is presented below.

6.2.1 | The functional outcome of MSC-derived sEVs in bone regeneration

Multiple animal models have shown that MSC-EVs stimulates neovascularization and bone repair (Table 29). Out of these investigations, the most often used approach for EV therapy is locally injecting native EVs in a liquid mixture.[210,233,238,240,919,930–932] One study demonstrated positive outcomes on bone regeneration even

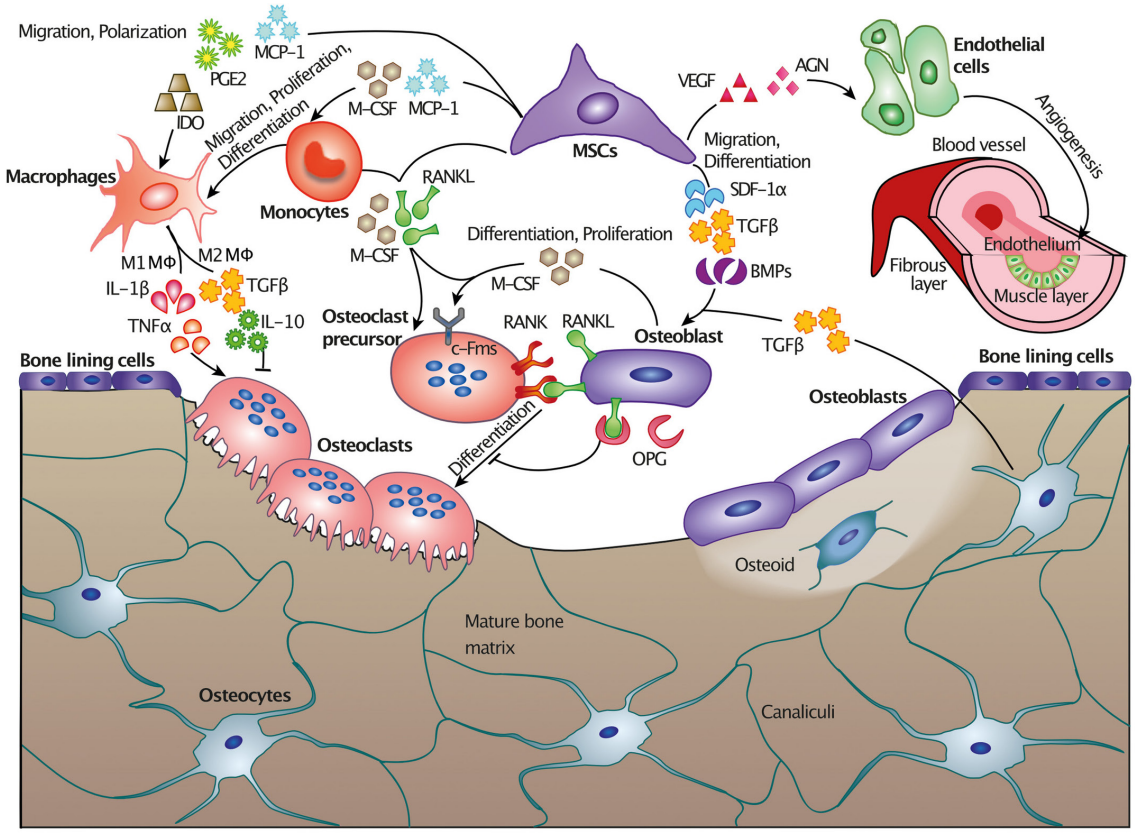

FIGURE 27 Multiple cellular and molecular interactions during bone regeneration. Some of the representative cellular interactions and responsible molecules are illustrated in the figure. (1) MSCs—OB/osteocytes: MSCs commit to osteoblasts and terminally differentiate to osteocytes. The secretion of SDF-1α, TGF-β and BMPs promotes the migration and differentiation of osteoblastic progenitor cells. (2) MSCs—Mo/Mϕ: MSCs regulate migration, proliferation, differentiation, and polarization of monocytes/macrophages via secretion of MCP-1, M-CSF, PGE2 and IDO. (3) MSCs/OB—Mo/OC: MSCs/osteoblasts interact with the osteoclastic lineage via secretion of M-CSF, RANKL and OPG, which regulate the proliferation, differentiation, and activation of osteoclasts. (4) Mo/MΦ—OC: Macrophages differentially influence the activity of osteoclasts via secretion of pro- or anti-inflammatory cytokines, depending on the Mϕ phenotypes. (5) MSCs—EC: MSC-secreted VEGF and AGN promote angiogenesis via increased proliferation, migration, and tube formation of endothelial cells. AGN, angiostatin; BMPs, bone morphogenetic proteins; EC, endothelial cell; IDO, indoleamine 2,3-dioxygenase; IL-10, interleukin 10; IL-1β, interleukin 1β; M1 Mϕ, pro-inflammatory Mϕ; M2 Mϕ, anti-inflammatory Mϕ; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage colony-stimulating factor; Mo, monocyte; Mϕ, macrophage; OB, osteoblast; OC, osteoclast; OPG, osteoprotegerin; PGE2, prostaglandin E2; RANK, receptor activator of nuclear factor-κB; RANKL, RANK ligand; SDF-1α, stromal cell-derived factor 1α; TGF-β, transforming growth factor-β; TNFα, tumor necrosis factor-α; VEGF, vascular endothelial growth factor. Reprinted with permission from Wang and Thomsen.[934]

when a systematic tail vein injection was utilized.[928] Commonly, EVs were loaded to various biomaterials including β-TCP,[922,923] PLA,[924] decalcified bovine bone matrix scaffolds,[935] or encapsulated in hydrogel[226,916,920] or collagen sponges.[933]

These combined findings show that MSC-EVs directly support bone regeneration by interacting with bone cells, namely those belonging to the MSC-osteoblast-osteocyte lineage. MSC-Exos from diverse origins have been shown to impact osteoblast proliferation, migration, differentiation, and mineralization.[916,922–926,929,936,937] Additionally, current research has revealed that MSC-EVs upregulate VEGFA and VEGFR2 expression thereby supporting both osteogenesis and angiogenesis during the process of bone regeneration.[924,927]

One of the first vital stages of cell–surface interactions and bone-regenerating process associated with implanted prostheses is cell adhesion.[938,939] MSC attachment to titanium surfaces was enhanced by implant surface-immobilized MSC-EVs, which also had an impact on adherent MSC behavior.[940] Furthermore, MSC-EVs protected bone-forming osteoblasts from harm during challenged environments such as during implant placement.

Several cargo components and recipient cell molecules have been investigated within EVs to determine the molecular mechanisms during bone regeneration.[936] MSC-EVs have been shown to transfer osteogenesis-related microRNAs to activate osteogenic differentiation. VEGF and RUNX2 levels increased, as did osteogenic differentiation.[210] Another study linked the pro-osteogenic

TABLE 29 MSC-derived sEVs in bone and cartilage regeneration.

sEVs and delivery routes	MSC source	Pretreatment of MSCs or sEVs	Experimental model	sEV administration	Functional outcome	References
Native sEVs Injection of suspension	Human BM	–	Femoral shaft fracture in C57BL/6 wild-type and $CD9^{-/-}$ mice	Local injection into the fractured part at 1 and 8 days after fracture	Promoted fracture healing in wild-type mice and rescued impaired fracture healing in $CD9^{-/-}$ mice	919
	Murine BM and human BM	–	Osteogenesis imperfecta animal model in G610 mice	Tail vein injection weekly for 4 weeks	Improved bone growth as indicated by increased bone length in both femora and tibiae	928
	AT	–	Ligature-induced periodontitis model in male albino Wistar rats	Local injection into pockets as an adjunctive treatment	sEV treatment showed promising periodontal regeneration as indicated by formation of highly organized proliferating periodontal ligament tissue and well-formed dense healthy bone in the periodontal ligament space	932
	Human ESCs	–	Critical-sized osteochondral defect on trochlear grooves of the distal femurs in female SD rats	Intra-articular injection weekly for up to 12 weeks	Promoted osteochondral regeneration as indicated by complete restoration of cartilage and subchondral bone	930
	Human ESCs	–	Critical-sized osteochondral defect on trochlear grooves of the distal femurs in female SD rats	Intra-articular injection weekly for up to 12 weeks	Accelerated cartilage repair, increased cellular proliferation and M2 macrophage infiltration, reduced cellular apoptosis and inflammatory cytokine secretion, and enhanced matrix synthesis	931
	Murine BM	–	Collagenase-induced OA model in C57BL/6 mice	Intra-articular injection at Day 7	Protected cartilage and bone from degradation induced by collagenase as indicated by increased cartilage thickness and bone volume	210
	Human ESCs	–	Destabilization of the medial meniscus surgery induced OA model in C578L/6J mice	Intra-articular injection every 3 days for 4 weeks	Promoted recovery of cartilage destruction as indicated by lower OARSI score and increased expression of Col II	233

TABLE 29 (Continued)

sEVs and delivery routes	MSC source	Pretreatment of MSCs or sEVs	Experimental model	sEV administration	Functional outcome	References
	Infrapatellar fat pads from OA patients	–	Induced OA model by surgical destabilization of the medial meniscus in male C578L/6 mice	Intra-articular injection twice per week for 4 or 6 weeks	Protected articular cartilage from damage and ameliorate gait abnormality as indicated by reduced OARSI score, reversed increase in COL2 expression and downregulated ADAMTS5 and MMP13 expression	240
	Human ESCs	–	Induced TMJ OA model by injection of monosodium iodoacetate in SD rats	Intra-articular injection weekly for up to 8 weeks	Suppressed pain and modulated early gene expression changes in TMJ condylar cartilage tissue, reversed TMJ degeneration as indicated by restored matrix synthesis, alleviated subchondral bone deterioration as indicated by restored bone volume and architecture, suppressed inflammation as indicated by reduced IL-1β+ and iNOS+ cells, promoted proliferation and reduced apoptosis as indicated by increased PCNA+ cells and decreased CCP3+ apoptotic cells	238
Material carrier	Human iPSCs	–	Critical-sized calvarial bone defects in osteopenic animal model using ovariectomized SD rats	Implantation of β-TCP scaffold with lyophilized sEVs in the defect site	Dose-dependently promoted bone regeneration and neovascularization in the defect site as indicated by an increased ratio of BV/TV, BMD, area of new bone formation and mineralization, area and number of vessels, and expression of the osteogenic markers OCN and OPN and the angiogenic marker CD31	922
	Human iPSCs	–	Critical-sized calvarial bone defects in SD rats	Implantation of β-TCP scaffold with lyophilized sEVs in the defect site	Dose-dependently enhanced bone regeneration in the defect site as indicated by an increased ratio of BV/TV, BMD, area of new bone formation and mineralization, and expression of the osteogenic marker OCN	923
	Human gingiva tissue	–	Cortical calvaria bone tissue damage in male Wistar rats	Implantation of 3D printed PLA scaffold enriched with sEVs or both sEVs and MSCs to cover the damaged area	Combination of 3D-PLA with enriched sEVs and MSCs improved bone healing as indicated by higher positive staining of calcium, increased vascularization, higher rate of regeneration and integration level at the damaged site	924

(Continues)

TABLE 29 (Continued)

sEVs and delivery routes	MSC source	Pretreatment of MSCs or sEVs	Experimental model	sEV administration	Functional outcome	References
	SD rat BM	–	Subcutaneous bone formation model in nude mice	Subcutaneous implantation of sEV functionalized DBM scaffold pre-coating with fibronectin and with or without seeding of osteogenic-induced MSCs	sEV functionalized DBM showed pro-angiogenic activity as indicated by increased CD31+ vessel formation. However, only combination of sEV functionalized DBM and MSCs showed enhanced bone regeneration as indicated by increased staining of new bone, BV and ratio of BV/TV	935
	Human AT	–	Calvarial defect in male SD rats	Implantation of sEV-loaded hydrogel in the defect site	Promoted bone regeneration as indicated by micro-CT analysis and histology examination	916
	Human umbilical cord	–	Stabilized fracture in femur of male Wistar rats	Injection of sEV-embedded HyStem-HP hydrogel near the fracture site	Enhanced bone healing and angiogenesis at the fracture site as indicated by increased callus formation, BMD, BV, BV/TV, vessel volume, number of CD31+ blood vessels, maximum mechanical load and bending stiffness	920
	Human iPSCs	–	Surgically created periodontal intrabony defect in SD rats	Implantation of sEV-loaded collagen sponge in the defect site	Promoted periodontal regeneration with enhanced bone growth, increased functional PDL length and increased cellular infiltration and proliferation at the defect site as indicated by histological examination and micro-CT analysis	933
	Human iPSCs	–	Articular full-thickness cartilage defect in New Zealand rabbits	Injection of sEV suspension or sEV-embedded in situ—formed or in vitro—preformed hydrogel glue to the defect site	In situ-formed hydrogel glue containing sEVs had best performance promoting cartilage repair and cartilage-hydrogel integration as indicated by uniform and well-organized articular cartilage structure, distribution of abundant chondrocytes in newly formed tissue, positive staining of Safranin O and Col II	226

TABLE 29 (Continued)

sEVs and delivery routes		MSC source	Pretreatment of MSCs or sEVs	Experimental model	sEV administration	Functional outcome	References
Modified sEVs	Injection of suspension	Rabbit BM	Transfection for expression of mutant HIF-1α	Steroid-induced avascular necrosis of femoral head in rabbits	Local injection of single-dose sEVs into the femoral head	Promoted bone regeneration and neovascularization in the necrotic region as indicated by massive trabecular tissue generation, increased staining of newborn cartilage and increased density of CD31+ micro vessels	929
		Human umbilical cord	Hypoxic condition	Femoral fracture model in mice	Local injection of single-dose sEVs near the fracture	Promote bone fracture healing primarily via enhanced angiogenesis indicated by increased volume of callus bridging the fracture gap, vessel volume, vessel number, expression of endothelial markers CD31 and endomucin and proliferation marker Ki67	921
	Material carrier	Human AT	Osteoinduction for 2 days	Critical-sized calvarial bone defects in male BALB/c mice	Implantation of an sEV-immobilized PLGA/pDA scaffold in the defect site	Increased bone formation and recruitment of SSEA-4+/CD45− MSCs at the defect site as indicated by increased new bone volume, collagen expression and expression of the osteogenic markers RUNX2 and OCN	925
		Human AT	Transfection for overexpression of miR-375	Calvarial defect in male SD rats	Implantation of sEV-loaded hydrogel in the defect site	Enhanced bone regeneration as indicated by increased ratio of BV/TV, BMD, staining of new bone and expression of the osteogenic markers OCN and BMP2	916
		Human gingiva tissue	Coating sEVs with branched PEI by using noncovalent layer-by-layer protocol	Cortical calvaria bone tissue damage in male Wistar rats	Implantation of 3D printed PLA scaffold carried with native sEVs or PEI-coated sEVs to cover the damaged area	Improved bone healing as indicated by new bone formation inside the scaffold structure and presence of blood vessels around the new bone deposition area. PEI-engineered sEVs showed better healing effects	926
		Human PDL tissue	Coating sEVs with branched PEI by using noncovalent layer-by-layer protocol	Cortical calvaria bone tissue damage in male Wistar rats	Implantation of 3D collagen membrane carried hPDLSCs and enriched with native sEVs or PEI-coated sEVs to cover the damaged area	Both native and PEI-engineered sEVs promoted vascularization as indicated by expression of the angiogenesis markers VEGFA and VEGFR2, however, PEI-sEVs improved bone regeneration and integration as indicated by the distribution of OB and OC in the naïve bone, and quantification of bone parameters including BV, BS, BV/TV, and BS/TV	927

Note: Reprinted with permission from Wang and Thomsen.[934]

Abbreviations: ADAMTS5, a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif 5; AT, adipose tissue; BM, bone marrow; BMD, bone mineral density; BMP2, bone morphogenetic protein 2; BS, bone surface; BV/TV, bone volume/total bone volume; CCP3, cyclic citrullinated peptide 3; Col II, type II collagen; ESC, embryonic stem cell; HIF-1α, hypoxia-inducible factor-1α; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; iPSC, induced pluripotent stem cell; MMP13, matrix metallopeptidase 13; OA, osteoarthritis; OARSI score, osteoarthritis research society international score; OB, osteoblasts; OC, osteoclasts; OCN, osteocalcin; OPN, osteopontin; PCNA, proliferating cell nuclear antigen; PDL, periodontal ligament; RUNX2, runt-related transcription factor 2; SD rat, Sprague–Dawley rat; TMJ, temporomandibular joint; VEGFA, vascular endothelial, growth factor A; VEGFR2, vascular endothelial growth factor receptor 2.

activities of MSC-EVs to their enrichment of Wnt3a and targeting of the Wnt signaling pathway, one of the most important signaling pathways regulating osteogenic development.[941] Previous authors [653] demonstrated that MSC-EVs also increased MSC osteogenic differentiation by activating the PI3K/Akt signaling pathway.[942,943] A summary of data is found in Table 29. Furthermore, Part III of this publication series further highlights the number of studies on exosomes produced from tooth tissues for bone regeneration.

6.3 | Cartilage/joint/tendon regeneration

In orthopedics, treating cartilage abnormalities such as osteoarthritis (OA) and osteochondral defects (OCD) continues to be very difficult and quite unpredictable. An estimated 654 million persons worldwide suffered from knee OA in 2020 and that number is only expected to increase.[944]

The two primary factors increasing the prevalence and incidence of OA are an aging population and rising obesity rates.[945] Articular cartilage degrades as a result of OA, a chronic inflammatory condition that causes joint stiffness and discomfort.[946] OA does not only affect the articular cartilage but also the synovium, subchondral bone, and ligaments around the joints.[947] The development of OCDs occurs when OA-related cartilage lesions impact the subchondral bone.[948] Based on the inflammatory component of OA, exosomes have been investigated as a means to repair bone cartilage, joints and tendons.

6.3.1 | In vivo delivery and exosome uptake

Avascular and alymphatic tissue makes up cartilage.[949] Therefore, exosomes are not appropriate for intravenous infusion for the treatment of cartilage abnormalities, unlike in other tissue injuries. Essentially, since intra-articular injection improves bioavailability and decreases off-target effects (as a whole for any biomaterial), exosome delivery to cartilage is performed locally. To date, all of the included clinical trials have therefore been performed by injecting exosomes directly into the afflicted joint with or without a scaffold.[950] To regenerate cartilage damage, several studies utilized a single injection, while others performed a series of injections (Table 30). Since no studies examined the therapeutic effects of single versus numerous injections, it is still unknown if multiple injections are more advantageous than single injections for cartilage regeneration. Cosenza and colleagues[210] as well as Wang et al.[80] suggested that exosomes administered intraarticularly may be visibly kept within the cartilage tissue even 1 month post-injection. This is most likely because exosomes were directly administered to the target site (cartilage is avascular and alymphatic, therefore exosomes are cleared slower). Exosomes may also remodel resident or injured cells by transferring bioactive molecules that activate regenerative mechanisms, thereby inducing cellular reprogramming.[951–953]

Ng et al.[954] conducted a comprehensive review on the use of exosomes in cartilage regeneration, resulting in a summary of 29 studies (Table 30 and illustrated in Figure 28). Direct injection without a carrier seems to be a method most preferred, although a few studies injected exosomes into the damaged cartilage tissues using a scaffold.[226,239,955] A scaffold has been discussed as being capable of distributing the exosomes more evenly over time and has been shown to prolong the delivery of exosomes over a longer duration. Moreover, it has been suggested that the combination of exosomes with biomaterials might provide a synergistic impact, enhancing the process of cartilage regeneration. According to Liu et al.,[955,956] in situ hydrogel glue and iPSC-MSC-Exos promoted cartilage regeneration in combination better than either group alone. The group that underwent in situ iPSC-MSC exosome hydrogel tissue patch implantation displayed consistent and well-structured articular cartilage composition, supporting histological results. In vitro research further has shown that exosomes help chondrocytes proliferate and migrate, inhibit apoptosis and the production of pro-inflammatory markers.[210,931,955–957]

6.3.2 | EVs for tendon repair

EVs and exosomes have also been utilized for tendon repair.[967] In sports and physical activities, tendon injuries are common where the recovery from injury is slow when compared to other tissues owing to a lack of blood flow. With a high risk of re-injury and the creation of scar tissue, the outcomes of conservative therapies and surgical interventions are not optimal. With 4 million new cases globally each year, tendon and ligament injuries account for 30% of all musculoskeletal consultations and represent a substantial economic and social burden.[968] Tendon healing has been documented when MSCs have been applied to damaged tendons. According to recent research, MSCs facilitated tendon healing owing to their secretion of EVs/exosomes.[967]

To date, nine investigations utilizing MSC-EVs have demonstrated positive outcomes on tendon and ligament healing. Several benefits have been reported by clinicians using MSC-EVs from cell-based therapies when it comes to treating tendon and ligament disorders including minimal immunogenicity, good stability, no issues with cell viability after implantation, no danger of uncontrolled activity or differentiation of transplanted cells, and no risk of persistence as permanent grafts following treatment discontinuation. Because the cellular components are missing in EVs, platelet-rich plasma/fibrin (PRP/PRF) has been proposed as a delivery vehicle exhibiting benefits in treating tendon and ligament issues.[969–973] Numerous review articles have highlighted the impact of EVs for treating tendons and ligaments, including the use of platelet concentrates.[969–973]

The transplantation of rat EVs produced from bone marrow microvascular cells was shown to enhance the repair of the rat Achilles tendon 30 days after damage in a dose-dependent manner, resulting in improvements to the tendon architecture, fiber structure,

TABLE 30 Summary of efficacy and safety findings.

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Zhang et al.[930]	SD rats Surgically induced OCD	Multiple intra-articular injections after surgery and thenceforth weekly	• Exo group: 100 μg/100 μL of ESC-MSC-Exos • Contralateral control: 100 μL PBS • Un-operated control	Week 6 or 12 post-surgery	• Exo group demonstrated almost complete neotissue filling with good surface regularity and complete integration of neotissue with surrounding cartilage by 12 weeks	Not reported	• Exo group exhibited almost complete regeneration and bonding of cartilage and underlying subchondral bone after 12 weeks • Distinctly higher modified O'Driscoll histological scores in the Exo group • Exo group showed hyaline cartilage formation with high amount of GAG, Col II, and low amount of Col I	No detrimental responses were observed in all animals
Cosenza et al.[210]	C57BL/6 mice Collagenase-induced OA	Single intra-articular injection at day 7 after OA induction	• Cell group: 2.5×10^5 BMSCs/5 μL • MP group: 500 ng/5 μL of BMSC-microvesicles • Exo group: 250 ng/5 μL of BMSC-Exos • OA group • Healthy control	Day 42 post-collagenase induction	Not reported	• CLSM showed structural improvement in articular cartilage which comparable with healthy control group in all treatment groups • μCT showed higher bone volume, lower bone degradation, lower osteophyte formation and lower calcification of menisci and ligaments in all treatment groups compared with the OA group	• Exo group showed the greatest improvement with the lowest OA scores	Not reported
Liu et al.[226]	New Zealand rabbits Surgically created OCD	Scaffold implantation or single intra-articular injection immediately after surgery	• EHG group: 20 μL in situ formed EHG tissue patch containing 1×10^{11}/mL iPSC-MSC-Exos • HG group: 20 μL in situ formed HG tissue patch • Pre-EHG group: 20 μL in vitro preformed EHG containing 1×10^{11}/mL iPSC-MSCs-Exos • Inj-Exo group: 20 μL of 1×10^{11}/mL iPSC-MSCs-Exos suspension • OA group: Saline rinsing	Week 12 post-surgery	• EHG group showed the best repair with smooth surface with white regenerated tissue fully filled the defects and integrated with surrounding cartilage	• OCT displayed uniform and well-organized articular cartilage structure in EHG group	• EHG group has the highest ICRS score and the neotissue was almost entirely hyaline cartilage (strong safranin O and Col II staining, weak Col I staining)	Not reported

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Tao et al.[230]	SD rats Surgically induced OA	Multiple intra-articular injections on the first day of week 5–8 after surgery	• Exo group: 100 μL of 10^{11} SM-MSC-Exos particles/mL • Exo-miR-140-5p group: 100 μL of 1011 miR-140-5p overexpressed SM-MSC-Exos particles/mL • OA group: Saline • Healthy control: Saline	Week 12 post-surgery	Not reported	Not reported	• Exo-miR-140-5p group showed the lowest OARSI assessment scores • Significant increased chondrocyte count, higher Col II and aggrecan expression, and lower Col I in the Exo-miR-140-5p group compared with the Exo and OA groups	No adverse events occurred
Wang et al.[233]	C57BL/6J mice DMM induced OA	Intra-articular injections at week 4 after surgery (once for Cell and Cell-OA group; multiple injections every 3 days for 4 weeks for Exo and Exo-OA group)	• Cell group: 5 μL of 1×10^{6} ESC-MSC suspension • OA group: 5 μL of PBS • Sham control • Exo group: 5 μL ESC-MSC-Exos • OA group: 5 μL of PBS • Sham control	Week 8 post-surgery	Not reported	Not reported	• Exo group exhibited similar regenerative effect as Cell group • Exo group revealed milder OA pathologycompared with the OA group which was concomitant with lower OARSI scores and stronger Col II staining and weaker ADAMTS5 and aggrecan neoepitope staining	Not reported
Zhu et al.[229]	C57B/L10 mice Collagenase-induced OA	Multiple intra-articular injections on day 7, 14 and 21 after collagenase administration	• iPSC-MSC-Exo group: 8 μL of 1×10^{10} particles/mL iPSC-MSC-Exos • SM-MSC-Exo group: 8 μL of 1×10^{10} particles/mL SM-MSC-Exos • OA group: 8 μL of PBS • Normal control: 8 μL of PBS	Day 28 post-collagenase induction	• No significant differences in ICRS macroscopic analysis scores among the normal, iPSC-MSC-Exo and SM-MSC-Exo groups, but significantly higher than the OA group	Not reported	• Neotissue of iPSC-MSC-Exo group presented smooth cartilage, regular cellular organization, and normal proteoglycan content that similar to control group; SM-MSC-Exo exhibited moderate • No significant differences in OARSI scores between the iPSC-MSC-Exo and normal group, but notable lower than the SM-MSC-Exo and OA groups • More intense Col II staining in the iPSC-MSC-Exo group compared with the SM-MSC-Exo group	Not reported

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Mao et al.[149]	C57B/L10 mice Collagenase-induced OA	Multiple intra-articular injections on day 7, 14 and 21 after collagenase administration	• Exo group: 15 μL of 500 μg/mL BMSC-Exos • Exo-miR-92a-3p group: 15 μL of 500 μg/mL miR-92a-3p overexpressed BMSC-Exos • OA group: 15 μL of PBS • Healthy control: 15 μL of PBS	Day 28 after collagenase induction	Not reported	Not reported	• Exo-miR-92a-3p group demonstrated significant reduced severity of cartilage matrix loss with higher Col II and aggrecan, and lower Wnt5a and MMP13 expressions in both gene and protein levels compared to the Exo and OA groups	Not reported
Wang et al.[254]	SD rats Surgically induced OA	Intra-articular injection	• Exo group: 100 μL of 1×10^{11} particles/mL MSC-Exos • TGF-β1-Exo group: 100 μL of 1×10^{11} particles/mL TGF-β1-MSC-Exos • TGF-β1-NC-Exo group: 100 μL of 1×10^{11} particles/mL TGF-β1-MSC-NC-ExosTGF-β1-miR135b inhibitor-Exo group: 100 μL of 1×10^{11} particles/mL TGF-β1-MSC-miR135b inhibitor-Exos	Week 12 post-surgery	Not reported	Not reported	• Significant lower OARSI scores in the TGF-β1-Exo group than the Exo group, with high OARSI scores in the TGF-β1-miR135b inhibitor-Exo group • TGF-β1-Exo group showed elevated number of chondrocytes, while dropped in chondrocyte number was recorded in the Exo and TGF-β1-miR135b inhibitor-Exo groups	Not reported
Zhang et al.[931]	SD rats Surgically induced OCD	Multiple intra-articular injections immediately after surgery on weekly basis	• Exo group: 100 μg/100 μL ESC-MSC-Exos • Contralateral control: 100 μL PBS	Week 2, 6, or 12	Not reported	Not reported	• Exo group demonstrated predominately hyaline cartilage regeneration (mostly Col II and very low Col I expression) and complete integration of neotissue with adjacent native cartilage with a smooth surface regularity and complete regeneration of subchondral bone at Week 12 • Wakitani scores of Exo group decreased from week 2 to 12 and the results were significantly lower than the contralateral control • Enhanced proliferation, attenuated apoptosis, increased M2 macrophages and reduced M1 macrophages in both cartilage andsynovium tissues, and decreased in M1-associated cytokines, that is, IL-1β and TNF-α, in synovial fluid of the Exo group	Not reported

(Continues)

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Chen et al.[239]	New Zealand White rabbits Surgically induced OCD	3D printed scaffold implantation	• ECM/GelMA group: ECM/GelMA scaffold • GelMA group: GelMA scaffold • ECM/GelMA/Exo group: 3D printed ECM/GelMA/BMSC-Exo scaffold • OA group: Untreated	Week 6 or 12 post-surgery	ECM/GelMA/Exo group exhibited smooth and intact tissues and gave the highest ICRS macroscopic analysis scores	• MRI scanning demonstrated smooth neo-cartilage and great defect filling in both ECM/GelMA and ECM/GelMA/Exo groups • μCT displayed increased ratio of bone volume to tissue volume, trabecular thickness, and ossified tissues in the subchondral bone of both ECM/GelMA and ECM/GelMA/Exo groups	• ECM/GelMA and ECM/GelMA/Exo groups showed hyaline-like cartilage regeneration in the defect sites • ECM/GelMA/Exo group has higher ICRS visual histological scores at week 12 • Increased Col II and decreased of MMP13 expression in the synovial membrane of ECM/GelMA and ECM/GelMA/Exo groups ECM/GelMA/Exo group expressed the lowest MDA levels	No apparent pathological effects in myocardium, liver, and kidney 1 to 2 weeks after transplantation
Liu et al.[956]	New Zealand White rabbits Surgically induced OA	Multiple intra-articular injections once a week	• Exo group: 100 μg/mL PRP-Exos • PRP-As group: 100 μg/mL activated PRP • OA group: Normal saline • Control: Normal saline	Week 6 after surgery	Not reported	Not reported	• Exo group exhibited more regular arrangement of chondrocytes, clearer tidal line, reduced hyperplasia on articular cartilage surface and lower OARSI scores than the PRP-As and OA groups Exo group showed increased expression of Col II and RUNX 2	No adverse events occurred
Wu et al.[240]	C57BL/6 mice DMM induced OA	Multiple intra-articular injections twice a week, starting at week 4 after surgery	• Exo group: 10 μL of 10^{10} particles/mL IPFP-MSC-Exos • OA group: 10 μL PBS • Sham control: 10 μL PBS	Week 8 post-surgery	Improved gait pattern (CatWalk gait analysis) after 6 weeks of exosome treatment	• Obvious green, fluorescent dots (DiO-labeled IPFP-MSC-Exos) can be found at the defect sites	• Exo group showed integration of cartilage with smooth surface and lower OARSI scores confirming cartilage lesion was healed Exo group showed higher expression of Col II as well as lower expression of ADAMTS5 and MMP13	Not reported
Zhao et al.[958]		3 weeks of 10 μL antagomir pre-injection (once a week), starting at week 1 after surgery, followed by injection of Exos and antagomir twice a week for 4 weeks	• PBS + antagomir-NC group: 10 μL PBS + antagomir-NC • Exo + antagomir-NC group: 10 μL 10^{10} particles/mL IPFP-MSC-Exos + antagomir-NC • Exo + antagomir-100-5p group: 10 μL 10^{10} particles/mL IPFP-MSC-Exos + antagomir-100-5p	Week 8 post-surgery	Not reported	Not reported	• Exo + antagomir-100-5p group reversed the results of the Exo group	Not reported

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Zhang et al.[238]	SD rats MIA-induced TMJ-OA	Multiple intra-articular injections once a week, starting 2 weeks after OA induction	• Exo group: 100 μg/50 μL of ESC-MSC-Exos • OA group: 50 μL of PBS • Sham control: needle pricks	Week 2, 4, or 8 post-treatment	• HWT improved gradually in the Exo group and reached the baseline level of the sham group at Week 5	μCT showed Exo group restored subchondral bone volume and architecture at Week 8	• Exo group revealed significant reduced gene expressions of pro-inflammation (IL-1β), apoptosis (BAX), fibrosis (α-SMA) and pain (Substance P, CGRP, NGF, P75NTR, and TrkA) and upregulated TIMP 2 and downregulated ADAMTS5 in condylar cartilage tissues • Significant lower Mankin scores at Weeks 4 and 8 in the Exo group • Exo group showed smoother cartilage surface, improved cellularity, reduced fibrous cartilage thickening, minimal depletion of s-GAG in condylar cartilage lesion at Week 4 and marked restoration of TMJ condylar structure at Week 8 • Exo group has lesser $MMP13^+$ cells in condyle region at Week 4; lesser IL-$1\beta^+$ and $iNOS^+$ cells, higher proliferative $PCNA^+$ cells and lesser $CCP3^+$ apoptotic cells at Weeks 4 and 8	No adverse immune reactions observed

(Continues)

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Zheng et al.[959]	C57BL/6 mice Surgically induced OA	Multiple intra-articular injections once per week, starting 10 days after surgery	• Exo group: 200 μg of primary Chondrocyte-Exos • OA group: 20 μL saline • Sham control: Untreated	Week 4, 6, or 8 post-surgery	Not reported	μCT demonstrated lower subchondral bone mineral density and smaller osteophyte formation at the joint margins in the Exo group	• Both femoral and tibia cartilage of the Exo group showed nearly complete preservation • No obvious synovitis appearance in all groups • Exo group expressed marked repression in MMP13 staining and elevated Col II staining in joint samples • Significant lower OARSI scores in the Exo group • Exo group exhibited higher level of M2 macrophages infiltration in the synovium and cartilage tissues • Exo-miR-136-5p group showed lesser loss of cartilage matrix followed by the Exo and OA groups • Exo-miR-136-5p group revealed higher level of Col II and aggrecan gene and protein expressions, decreased in ELF3 and MMP13 gene and protein expression	Not reported
Chen et al.[247]	C57BL/6 mice Mechanical load induced OA	Single intra-articular injection immediately after mechanical induction	• Exo group: 100 μL of 10^{11} particles/mL BMSC-Exos • Exo-miR-136-5p group: 100 μL of 10^{11} particles/mL miR-136-5p overexpressed BMSC-Exos • OA group: Untreated • Normal control: Untreated	1 h after injury	Not reported	Not reported	• Exo-miR-136-5p group showed lesser loss of cartilage matrix followed by the Exo and OA groups • Exo-miR-136-5p group revealed higher level of Col II and aggrecan gene and protein expressions, decreased in ELF3 and MMP13 gene and protein expression	Not reported

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
He et al.[234]	SD rats MIA-induced OA	Multiple intra-articular injections once a week, starting 1 week after OA induction	• Exo group: 40 μg/100 μL BMSC-Exos • OA group: 100 μL of normal saline • Sham control: 100 μL of normal saline	Week 6 post-treatment	• Joint injuries were alleviated in the Exo group Thermal PWL and mechanical PWT improved at Weeks 2, 4 and 6 in the Exo group	In vivo imaging showed accumulation of PKH26 labeled BMSC-Exos in the joint cavity	• Articular cartilage of the Exo group regenerated, with small number of defects and fractures on cartilage surface • Exo group has significantly reduced OARSI scores • Exo group demonstrated notably increased in Col 2 protein expression level in chondrocytes and ECM, and decreased of MMP13 and Col 1 protein levels in cartilage tissue • Exo group showed reduced expression of CGRP and iNOS in DRG • Lower inflammatory cytokines (IL-1β, IL-6 and TNF-α) and higher anti-inflammatory cytokine (IL-10) in serum of Exo group	Not reported
Jin et al.[960]	SD rats Surgically induced OA	Intra-articular injection, starting 2 weeks after OA induction	• Exo group: BMSC-Exos • OA group: Normal saline	Week 7 post-treatment	Not reported	Not reported	• Lower observation and Mankin scores in the cartilage of the Exo group • Notably decreased in inflammatory factors, AKP content and oxidative stress injury indicators, but increased in SOD in synovial fluid of the Exo group • Cartilage tissue of Exo group showed significant reduced MMP13, OCN and COMP gene and protein expressions	Not reported

(Continues)

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Jin et al.[235]	Wistar rats Surgically induced OA	1-week intra-articular injection of treatments after surgery	• Exo-miR-26a-5p group: 250 ng/5 μL of miR-26a-5p overexpressed BMSC-Exos • Exo-miR-NC group: 250 ng/5 μL of miR-NC BMSC-Exos • OA group: Untreated • Sham control: UntreatedHealthy control: Untreated	Week 8 post-surgery	Not reported	Not reported	• Exo-miR-26a-5p group has less pathological changes with the concomitant of reduced synovial tissue proliferation and suppressed inflammation • Exo-miR-26a-5p group has lower MMP3 and MMP13 expression and higher apoptotic index in synovial cells • Notably increased of miR-26a-5p expression and declined of PTGS2 expression in synovial tissue of the Exo-miR-26a-5p group • Exo-miR-26a-5p group showed reduced serum IL-1β levels	Not reported
Liang et al.[961]	SD rats DMM induced OA	Multiple intra-articular injections post-injury, once per week	• Exo group: 100 μg of Exos particles in 100 μL PBS • Exo-miR140 group: 100 μg of Exo-miR140 particles in 100 μL PBS • CAP-Exo-miR140 group: 100 μg of CAP-Exo-miR140 particles in 100 μL PBSOA group: Untreated • Sham control: Untreated	Week 8 post-surgery	Not reported	Fluorescence microscopy showed that CAP-Exo-miR-140 mainly stayed in the articular cavity, while Exo-miR-140 distributed to other body parts and enriched in kidney	• CAP-Exo-miR140 group displayed smooth and flat cartilage surface, small joint space, proper cell alignment, normal subchondral bone and dense proteoglycan which was almost identical to the sham control and comparable OARSI scores with sham control • CAP-Exo-miR140 group suppressed the MMP13 and Adamts5 protein levels in cartilage tissue • Upregulation of miR-140 and downregulation of MMP13 gene expression in cartilage tissue in the CAP-Exo-miR140 group	Nontoxic to major organs (heart, liver, kidney, lung, and spleen)

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Liu et al.[955]	SD rats Surgically induced OCD	Intra-articular implantation	• Exo group: Col-Tgel hydrogel with BMSC-Exos • KGN-Exo group: Col-Tgel hydrogel with KGN-BMSC-Exos • Gel group: Col-Tgel hydrogel • OA group: Untreated • Normal control: Untreated	Weeks 4, 6, and 8 post-surgery	• Better cartilage regeneration in the KGN-Exo group as indicated by smoother articular surface and better integration of newly formed cartilage with adjacent host cartilage • KGN-Exo group exhibited higher ICRS macroscopic scores which were comparable with the normal group at 8 weeks	Not reported	• KGN-Exo group revealed better cartilage reconstruction with hyaline cartilage predominantly, corresponding to notable high ICRS visual histological scores • KGN-Exo group showed increased s-GAG in cartilage tissue started at week 2 More lubricin and Col II positive cells and less Col I positive cells in KGN-Exo group compared to other groups except for the normal control group	Not reported
Qiu et al.[248]	Mice Surgically induced OA	Not mentioned	• Exo-Cur group: Curcumin pretreated BMSC-Exos • Exo group: BMSC-Exos • OA group • Sham control	Not reported	Not reported	Not reported	• Exo-Cur group showed higher gene expression of miR-124 and miR-143 as well as lower protein expression of ROCK1, NF-kB and TLR9 that were similar to the sham control group Exo-Cur group has less apoptotic chondrocytes compared to the OA and Exo groups	Not reported
Wong et al.[962]	New Zealand white rabbits Surgically induced OCD	Multiple intra-articular injections at day 0, day 7 and day 14 post-surgery	• Exo + HA group: 1 mL of 3% (w/v) hyaluronic acid with 200 μg ESC-MSC-Exos • HA group: 1 mL of 3% (w/v) hyaluronic acid	Week 6 or 12 post-treatment	• Significant improvement in ICRS scores of Exo + HA group at week 6 and 12, associated with marked improvements of neotissue integration at the border zone • Exo + HA group displayed improved mean Young's moduli and stiffness of the repaired cartilage that approximated the normal tissue	Not reported	• Exo + HA group showed improvements in cartilage regeneration over time as confirmed by complete defect coverage by neotissue characterized by the presence of hyaline cartilage, normal cellularity and chondrocytic-like cells, high GAG and Col II deposition, and lower Col I deposition at week 12 Exo + HA group exhibited higher modified O'Driscoll scores than the HA group at week 6 and 12	No adverse events

(Continues)

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Yan and Wu[963]	New Zealand rabbits Surgically induced cartilage defect	Multiple intra-articular injections on a weekly interval	• 2D-Exo group: 500 μL of 1×10^{10} particles/mL 2D cultured UC-MSC-Exos • 3D-Exo group: 500 μL of 1×10^{10} particles/mL 3D cultured UC-MSC-Exos • OA group: 500 μL PBS	Week 4 post-treatment	• Significant improvement in ICRS macroscopic scores in the 3D-Exo group compared to the 2D-Exo and OA groups • 3D-Exo group demonstrated more neotissue formation with smoother surface and better integration with the native hyaline cartilage at the surrounding	Not reported	• 3D-Exo group displayed partly hyaline cartilage and the defects showed greater surface regularity and better thickness of cartilage than the 2D-Exo group • 3D-Exo group exhibited lower Wakitani score than the 2D-Exo and OA groups	Not reported
Zavatti et al.[964]	CD rats MIA-induced OA	Intra-articular injection 3 weeks after OA induction (once for Cell and OA groups; twice for Exo group with 10 days interval)	• Cell group: 50 μL of 5×10^{5} AFSCs • Exo group: 50 μL of 100 μg AFSC-Exos • OA group: 50 μL of glucose/PBS • Contralateral control	Week 3 Post-treatment	• Cell and Exo groups have higher pain tolerance, and the results were comparable to the normal control group	Not reported	• Exo group showed better cartilage regeneration as indicated by complete neotissue formation with good surface regularity compared to the cell-treated defects which exhibited few fissures on the cartilage surface • Uniformed GAG distribution was demonstrated in the Exo group • Both Exo and cell groups exhibited improved OARSI scores Cell group displayed more intense Col II staining, whereas Exo group showed more regular distribution of Col II	No adverse inflammatory responses were observed

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Zhang et al.[209]	SD rats Surgically induced OA	Intra-articular injection every 3 days for 4 weeks, starting at Week 4 Post-operation	• Exo group: 10 μL 1010 particles/mL BMSC-Exos • OA group: 10 μL PBS • Sham control	Week 4 post-treatment	Not reported	• μCT showed less cartilage degradation, near-normal chondrocyte morphology and distribution, and less osteophyte formation around the joint treated with Exo • Dil-labeled Exo were observed in the knee joint and taken up by the synovial cells	• Lower OARSI scores in the Exo group compared with the OA group • Exo group demonstrated upregulated chondrogenic gene expressions and downregulated hypertrophic gene expressions • Exo group has decreased synovial hyperplasia and cell filtration • Exo group has less M1-positive cells and more M2-positive cells • Exo group exhibited reduced pro-inflammatory cytokines (IL-1β, TNF-A) and increased anti-inflammatory cytokine (IL-10) in synovial fluidExo group showed significant reduction in synovitis scores	Not reported
Zhou et al.[236]	C57BL/6J mice Collagenase VII induced OA	Multiple intra-articular injections at Days 7, 14, and 21 after collagenase induction	• Exo group: BMSC-Exos • pExo group: polydactyly BMSC-Exos • OA group: Saline • Normal control	Day 28 post-collagenase VII injection	Not reported	Not reported	• pExo group alleviated cartilage damage evidenced by the significant lower OARSI scores than the OA and Exo groups	Not reported

(Continues)

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Wang et al.[965]	C57BL/6J mice Surgically induced OA	Single intra-articular injection at Week 4 post-operation	• Sham-Exo group: 200 μg sham-Exos • OA-Exo group: 200 μg OA-Exos • ATF4-OA-Exo group: 200 μg ATF4-OA-Exos • OA group • Sham control	Week 8 post-surgery	Not reported	μCT showed reduced osteophyte formation in Sham-Exo and ATF4-OA-Exo groups, while OA-Exo group displayed enlarged osteophytes	• Sham-Exo and ATF4-OA-Exo groups alleviated pathological injury of articular tissues observed in the OA group, whereby the ATF4-OA-Exo group exerted greater therapeutic effect and lesser proteoglycan loss • ATF4-OA-Exo group exhibited lower Mankin scores than the Sham-Exo group, while OA-Exo group aggravated the cartilage damage and exhibited the highest Mankin scores among all groups • ATF4-OA-Exo group gave stronger effect in upregulating Col II levels and downregulating MMP13 levels • ATF4-OA-Exo group was more potent in decreasing inflammatory cytokine levels in the cartilage ATF4-OA-Exo group partially restored the impeded autophagy of the OA cartilage	Not reported
Wang et al.[232]	BALB/C mice 4°C water stimulated OA	Multiple intra-articular injection once a day, starting from day 20 after OA induction	• Exo group: 30 μL of 10^{11} particles/mL SM-MSC-Exos • Exo-155-5p group: 30 μL of 10^{11} particles/mL miR-155-5p overexpressed SM-MSC-Exos • OA group: normal saline • Normal control	2 weeks post-treatment	Not reported	Not reported	• Exo-155-5p group revealed lower OARSI scores and higher chondrocyte number in femoral condyle • Exo and Exo-155-5p groups reversed the increased caspase-3 and decreased Col II expressions in OA femoral condyle sections, but Exo-155-5p was more effective	Not reported

TABLE 30 (Continued)

References	Animal models	Method of delivery	Treatment groups	Euthanasia	Efficacy outcome			Safety outcome
					Macroscopic and functional analysis	Imaging	Histological and biochemical analysis	
Yan et al.[966]	SD rats Surgically induced artilage defects	Multiple intra-articular injections on a weekly interval	• S-Exo group: 100 μL of 1 mg/mL rotary cell culture system cultured UC-MSC-Exos • si-Exo group: 100 μL of 1 mg/mL rotary cell culture system cultured siRNA H19 transfected UC-MSC-Exos • OA group: 100 μL PBS	Week 4 or 8	• S-Exo group revealed reduced pain with higher LWT at Week 3 • Defects covered with neotissue at Week 4 and were filled with uniform tissue and obscured boundaries at Week 8in the S-Exo group • S-Exo group showed the highest ICRS scores	• Defects of S-Exo group displayed similar intensity to the adjacent cartilage through MRI at Week 8 • S-Exo group exhibited the lowest T2 values at Weeks 4 and 8	• S-Exo group has the best surface regularity, highest glycosaminoglycan, most orderly tissues and best subchondral bone repair among the groups • S-Exo group has significant lower Wakitani scores compared to the other groups • S-Exo group displayed the highest matrix synthesis which consists mainly of Col II	Not reported

Note: Reprinted with permission from Ng et al.[954]

Abbreviations: ADAMTS, ADAM metallopeptidase with thrombospondin motifs; AFSC, amniotic fluid stem cell; AKP, alkaline phosphatase; BAX, Bcl-2 associated X protein; BMSC, bone marrow-derived mesenchymal stem/stromal cell; CAP, chondrocyte-affinity peptide; CCP3, cleaved caspase-3; CGRP, calcitonin gene-related peptide; CLSM, confocal laser scanning microscopy; col I, type I collagen; col II, type II collagen; COMP, cartilage oligomeric matrix protein; DMM, destabilization of medial meniscus; DRG, dorsal root ganglion; ECM, extracellular matrix; EHG, exosome encapsulating hydrogel; ELF3, E74-like factor 3; ESC-MSC, embryonic stem cell-derived mesenchymal stem/stromal stem/stromal cell; Exo, exosome; GAG, glycosaminoglycan; GelMA, gelatin methacrylate; HWT, head withdrawal threshold; ICRS, International Cartilage Repair Society; IL, interleukin; iNOS, inducible nitric oxide synthase; IPFP-MSC, infrapatellar fat pad-derived mesenchymal stem/stromal cell; iPSC-MSC, induced pluripotent stem cell-derived mesenchymal stem/stromal cell; KGN, kartogenin; LWT, leg withdrawal threshold; MDA, malondialdehyde; MIA, monosodium iodoacetate; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; MSC, mesenchymal stem/stromal cell; NC, negative control; NGF, nerve growth factor; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OCD, osteochondral defect; OCN, osteocalcin; OCT, optical coherence tomography; P75NTR, p75 neurotrophin receptor; PBS, phosphate-buffered saline; PCNA, proliferating cell nuclear antigen; PRP, platelet-rich plasma; PWL, paw withdrawal latency; PWT, paw withdrawal threshold; RUNX2, runt-related transcription factor 2; SD rat, Sprague–Dawley rat; SMA, smooth muscle actin; SM-MSC, synovial membrane-derived mesenchymal stem/stromal cell; SOD, superoxide dismutase; TGF-β1, transforming growth factor beta 1; TIMP, tissue inhibitor of metalloproteinase; TMJ, temporomandibular joint; TNF-α, tumor necrosis factor alpha; TrkA, tropomyosin receptor kinase A; UC-MSC, umbilical cord-derived mesenchymal stem/stromal cell; μCT, micro computed tomography.

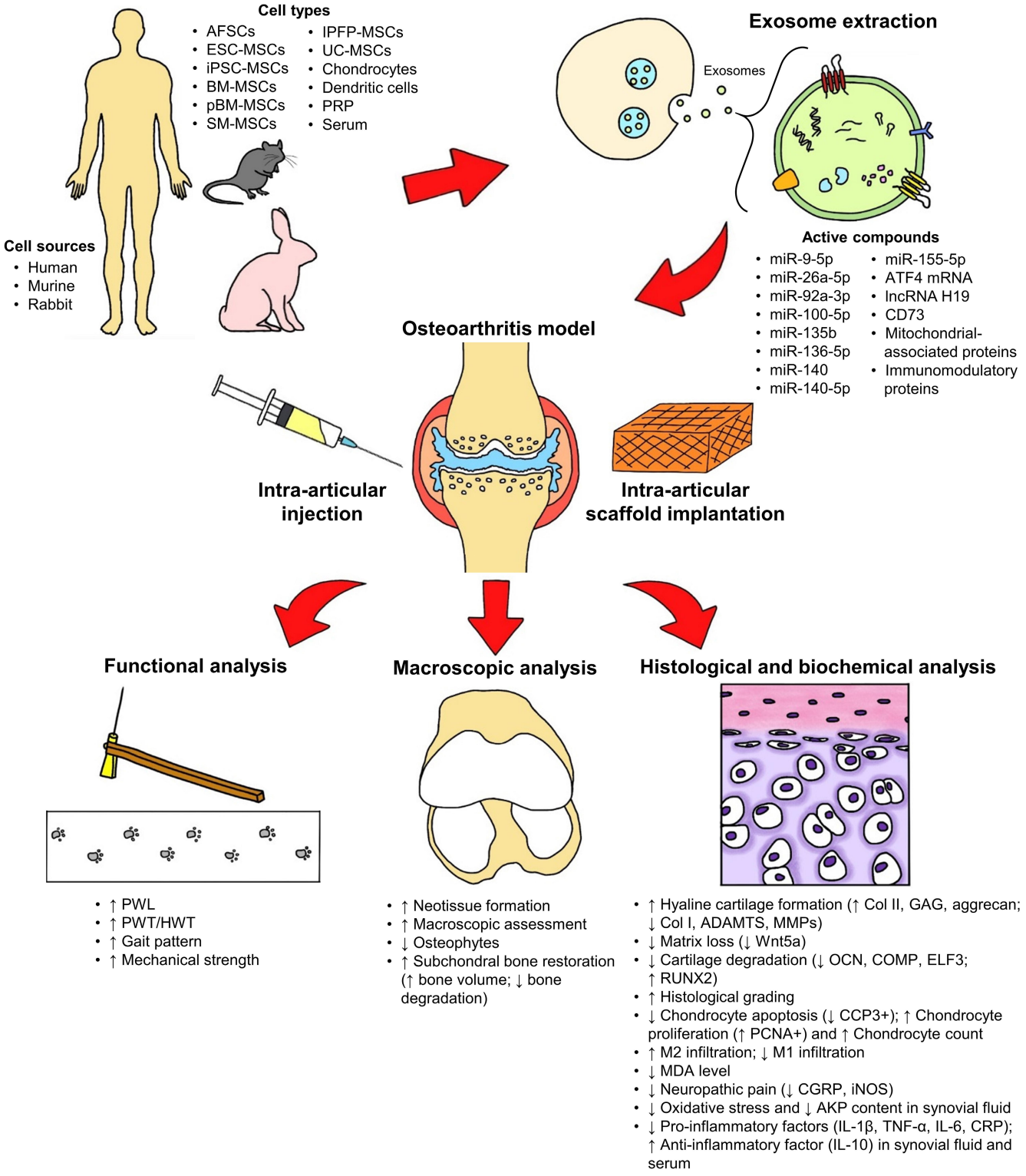

FIGURE 28 Overview of the studies. The exosomes tested in the included studies were derived from human, murine, or rabbit amniotic fluid stem cells (AFSCs), embryonic stem cell-derived mesenchymal stem/stromal cells (ESC-MSCs), induced pluripotent stem cell-derived MSCs (iPSC-MSCs), bone marrow-derived MSCs (BMSCs), polydactyly BMSCs, synovial membrane-derived MSCs (SM-MSCs), infrapatellar fat pad-derived MSCs (IPFP-MSCs), umbilical cord-derived MSCs (UC-MSCs), chondrocytes, dendritic cells, platelet-rich plasma (PRP), and serum. The exosomes were administered to the osteoarthritic joint through intra-articular injection or scaffold implantation. The exosomal bioactive compounds played an important role in cartilage and subchondral bone repair and regeneration. Overall, exosome therapy restored joint function, reduced joint pain, and improved the joint macroscopic, histological, and biochemical features. Reprinted with permission from Ng et al.[954]

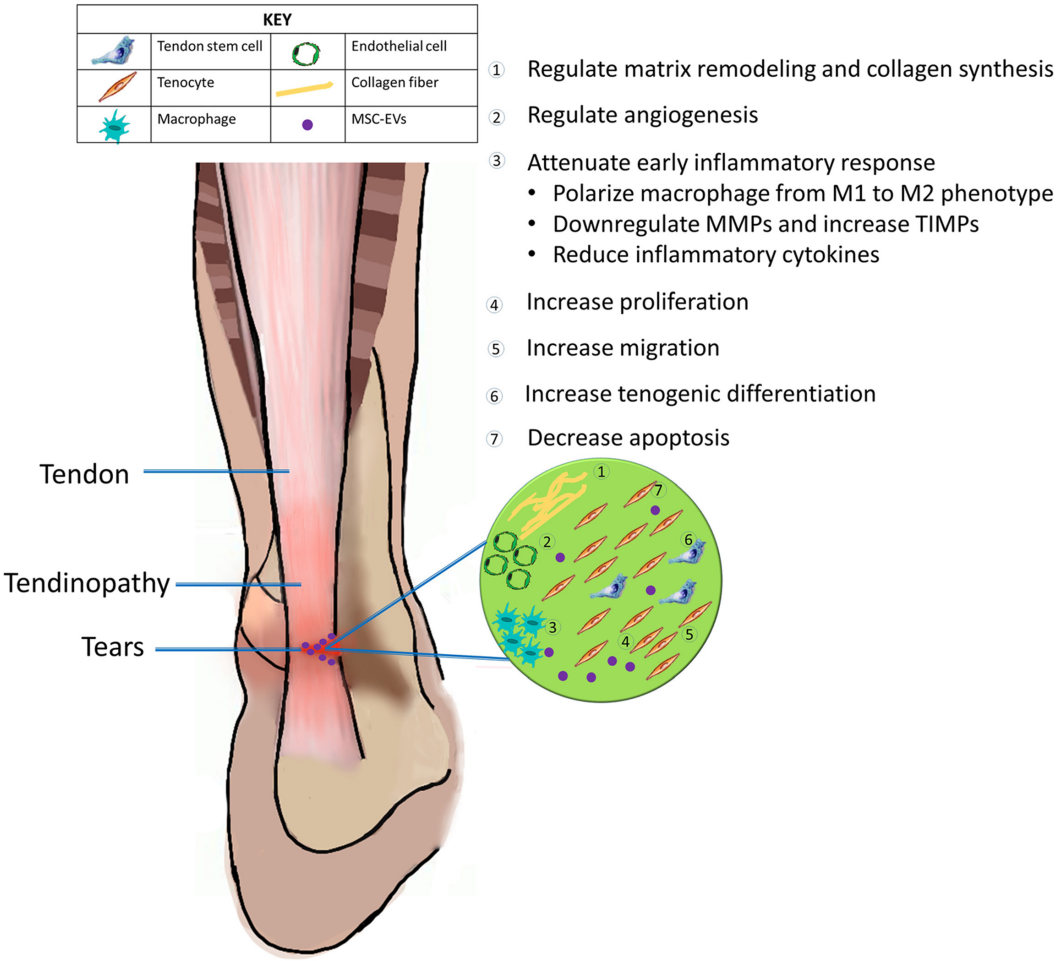

FIGURE 29 Mechanisms of MSC-EVs on tendon repair. Reprinted with permission from Liu (2021).[967]

and collagen type 1 expression.[974] The BMSC-EV group exhibited decreased expression of collagen type III and increased vascularity compared to both the PBS control group and the BMSC group, suggesting that the BMSC-EV group had superior healing quality.[974] Similarly, tendon recovery was faster in rats when fibrin glue was added to BMSC-EVs transplanted to the patellar tendon window incision than in either the fibrin glue alone or untreated groups. Evidence of this included more Col1a1 gene expression and better collagen fiber alignment 4 weeks after the damage.[974] Yu et al.[975] showed that the biomechanical and histological regeneration of the rat patellar tendon was greatly enhanced by the injection of BMSC-EVs in fibrin glue, indicating that BMSC-EVs may improve the biomechanical characteristics of damaged tendons. Another study found that local distribution of BMSC-Evs in the hydrogel improved tendon-bone healing in mice, with greater fibrocartilage and better biomechanical properties than the hydrogel-only and control groups.[974]

Intratendonous injections of exosomes from tendon-derived stem cells (TDSCs) was also shown to accelerate tendon regeneration both biomechanically and histologically in a collagenase-induced rat Achilles tendinopathy model.[976] It has been shown that part of the mechanism by which repair occurs is via macrophage polarization and immune cell regulation.[976] Previous research has shown that MSC-Exos have the ability to shift the macrophage response to tendon damage from an inflammatory M1 phenotype to a regenerative M2 phenotype via paracrine processes.[977–979] Figure 29 and Table 31 summarize and highlight the benefits of exosomes for tendon repair.

6.4 | Cutaneous wounds

A number of studies and systematic reviews have now pointed to the benefit of exosomes on cutaneous wound healing.[985–996] A study by Zeng and Liu pointed to a number of studies to date that have favored better healing with stem cell-derived exosomes.[995] In that study, exosomes were investigated on the many phases of wound healing. It was found that exosomes improved the hemostasis phase by favoring faster blood clot formation,[997] aided the inflammatory phase by decreasing inflammation and improving M2 macrophage polarization,[128,998] stimulated the proliferative phase by targeting fibroblast activity, improving collagen type III formation,[999] new vessel formation,[784] and lastly enhanced the remodeling phase by minimizing scarring.[720,779] (Table 32). Interestingly, a number of studies have further pointed to the benefit of exosomes on diabetic

TABLE 31 Studies investigating the therapeutic potential of MSC-EVs on tendon repair.

Animal model	EV (source/dosage/frequency)	Time point	Results	References
Achilles tendon transection and repair model in nude mouse	EEM (Human BMSC-derived EVs were used to educate human macrophages to M2 phenotype)/1×10^6/immediately after repair/once	Day 7 and Day 14 post-injury	EEM treatment substantially improved the biomechanical properties of the healing tendon but showed no improvement in collagen fiber organization. The EV or BMSC treatment showed biological responses had but have no effects on the biomechanical properties of tendon nor collagen fiber organization. The EEM treatment reduced the expression of type I collagen and type I/type III collagen ratio while the expression of type III Collagen remained unchanged compared to the injured control. The injection of EVs similarly reduced the expression of type I collagen in the healing tendon. However, it had no treatment effects on the expression of type III collagen and type I/type III collagen ratio	Chamberlain et al.[980]
A case study of a horse suffering from suspensory ligament injury	Allogeneic MVs derived from 5-azacytidine (AZA) and resveratrol (RES)-treated ASCs isolated from horse with metabolic syndrome/dosage not reported/twice (7 days after injury and 9 months after first injection)	10 months and 12 months after first injection	The application of MVs improved lesion filling, angiogenesis, and elasticity of injured tissue	Kornicka-Garbowska et al.[981]
Rat patellar tendon window injury model	Rat BMSC-EVs/25 μg in 10 μL fibrin glue/once	2 and 4 weeks post-injury	The local administration of BMSC-EVs promoted tendon healing with improvement in collagen fiber Alignment, expression of tendon matrix genes and tenogenic differentiation markers compared to the fibrin glue-only group and untreated group Inflammation and accumulation of apoptotic cells were suppressed while the numbers of tendon progenitor cells increased at the healing site	Shi et al.[974]
Rat Achilles tendon collagenase-induced tendinopathy model	Rat Achilles tendon TDSC-derived Ex/dosage not reported/twice a week at 1-week post-injury	5 weeks post-injury	The injection of exosome derived from TDSCs promoted tendon repair both histologically and biomechanically compared to the injury group and the treatment effects were comparable to the TDSCs treatment	Wang et al.[976]

TABLE 31 (Continued)

Animal model	EV (source/dosage/frequency)	Time point	Results	References
Rat Achilles tendon injury model	Rat BMSC-EVs/2.8×10^{12} or 8.4×10^{12}/once	30 days	BMSC-EVs accelerated tendon repair in a dose-dependent manner. Higher doses of BMSC-EVs produced better restoration of tendon architecture, tendon-fiber alignment, and lower vascularity. Higher concentration of EVs induced higher expression of collagen type I and lower expression of collagen type III compared to the PBS control group and BMSC group	Gissi et al.[969]
Mouse Achilles tendon two-third partial transection and repair model	Mouse naïve and IFN-γ-primed ASC-EVs in collagen sheet/$5–6\times10^{9}$ from 5×10^{5} ASCs/once	1, 3, and 7 days post-injury	Compared with the untreated control group, primed ASC-EVs, not their unprimed counterparts, further reduced the rate of post-repair tendon gap formation and rupture and promoted collagen formation at the injury site. Primed ASC-EVs, but not unprimed EVs, attenuated the early tendon inflammatory response after injury via modulation of the macrophage inflammatory response	Shen et al.[982]
Mouse Achilles tendon-bone reconstruction model	Mouse BMSC-derived Ex in hydrogel/dosage not reported/once	7 days, 14 days and 1 month post-surgery	At 1 month after surgery, there was more fibrocartilage in the exosome group than in the other groups. The biomechanical properties of the tendon-bone junction significantly improved in the exosome group	Shi et al.[983]
Rabbit rotator cuff repair	ADSC-derived Ex/dosage not reported/once	18 weeks post-surgery	The injection of Ex reduced fatty infiltration, increased the histological score with more fibrocartilage and improved biomechanical properties of the tendon-bone junction compared to the saline group	Wang et al.[984]
Rat patellar tendon window injury model	Rat BMSC-derived Ex in fibrin glue/20 μg in 10 μL/once	3 days, 1, 2, 4 weeks post-injury	The transplantation of Ex improved the histological scores, promoted the proliferation of resident tendon stem cells, enhanced the expression of tenomodulin and type I collagen as well as biomechanical properties of neotendon	Yu et al.[975]

Note: Reprinted with permission from Po and Liu.[967]

TABLE 32 Effects of mesenchymal stem cell exosomes on cutaneous wound healing.

Phase	Exosome source	Nomenclature	Related exosomal cargo	Secreted factors or expressed genes affected	Outcome	References
Hemostasis phase	Human mesenchymal stem cells (MSCs) from the umbilical cord	EVs	–	Phosphatidylserine (+)	Umbilical MSCs and extracellular vesicles derived from them have a reasonably high procoagulant potential	997
Inflammatory phase	Human jaw bone marrow-derived MSCs and bone marrow MSCs	Exosomes	miR-223	TNF-α ↓ IL-10 ↑	Accelerated wound healing in mice Induced M2 macrophage polarization ($CD206^+$ macrophage ↑)	998
	Human umbilical cord (UC)-MSCs	Exosomes	let-7b	TLR4, p-p65, iNOS ↓ p-STAT3, p-AKT, ARG1↑	Alleviated inflammation and enhanced diabetic cutaneous wound healing in rats Induced M2 macrophage polarization Inhibited TLR4 signaling pathway	128
	Human UC-MSCs	Exosomes	miR-181c	TNF-α, IL-1β, TLR4, p65, p-p65↓ IL-10 ↑	Reduced burn-induced inflammation in rats Reduced neutrophil and macrophage infiltration (MPO^+ cell, $CD68^+$ cell ↓) Inhibited TLR4 signaling pathway	135
	Human menstrual blood-derived MSCs (MenSCs)	Exosomes	–	iNOS ↓ ARG1, VEGF ↑	Resolved inflammation and ameliorate cutaneous non healing wounds in diabetic mice Induced M2 macrophage polarization	720
Proliferative Phase	Human bone marrow MSC-derived exosomes	Exosomes	TGF-β/Smad	TGF-β1, Smad2, Smad3, Smad4 ↓ TGF-β3, Smad7 ↑	Effectively promoted the cutaneous wound healing by inhibiting the TGF-β/Smad signal pathway	1000
	Human adipose MSCs (ASCs)	Exosomes	–	N-cadherin, cyclin 1, PCNA, collagen I/III, elastin ↑	Facilitated cutaneous wound healing via optimizing the characteristics of fibroblasts	779
	Human ASCs	Exosomes	–	Collagen I/II, TGF-β1/3, MMP1/3 α-SMA ↓	Promoted ECM reconstruction in cutaneous wound repair by regulating the ratios of collagen type III: type I, TGF-β3:TGF-β1, and MMP3:TIMP1, and by regulating fibroblast differentiation to mitigate scar formation	999
	Human fetal dermal MSCs	Exosomes	Jagged 1	Collagen I/III, elastin, fibronectin mRNA ↑	Promoted wound healing by activating the ADF cell motility and secretion ability via the Notch signaling pathway	1001
	Human UC-MSCs	Exosomes	Wnt4	CK19, PCNA, collagen I ↑	Stimulated the AKT pathway to protect immortalized keratinocytes from heat-induced apoptosis stimulated the AKT pathway to protect immortalized keratinocytes from heat-induced apoptosis	1002

TABLE 32 (Continued)

Phase	Exosome source	Nomenclature	Related exosomal cargo	Secreted factors or expressed genes affected	Outcome	References
	Human UC-MSCs	Exosomes	Akt, ERK, STAT3	HGF, IGF1, NGF, SDF1 ↑	Promoted the proliferation and migration of fibroblasts in normal and chronic wounds. This effect was positively correlated with the dose of exosomes	713
	Induced pluripotent stem cell-derived MSCs	Exosomes	–	Collagen ↑	Increased the secretion of collagen by HaCaT cells to accelerate skin cell proliferation	1003
	Adipose mesenchymal stem cells (ADSCs)	Exosomes	AKT/HIF-1α	–	Promoted the proliferation and migration of HaCaT cells by regulating the activation of the AKT/HIF-1α signaling pathway, thus promoting wound healing	1004
	Human UC-MSCs	Exosomes	–	PARP-1, PAR ↑	Suppressed HaCaT cell apoptosis induced by H_2O_2 by restraining the nuclear translocation of apoptosis-inducing factor (AIF) and promoting poly (ADP-ribose) (PAR) and poly ADP ribose polymerase 1 (PARP-1) expression	1005
	Human adipose-derived MSCs (adMSC-Exo)	Exosomes	miR-125a	Angiogenic inhibitor delta-like 4 (DLL4) ↓	Transferred miR-125a to endothelial cells and promoted angiogenesis by repressing DLL4	1006
	Mouse BM-MSCs	Exosomes	miR-17 miR-23a miR-125b	TNF-α, IL-1β, iNOS, TLR4, IRAK1, p65 ↓ ARG1, IL-10, TGF-β ↑	Decreased the threshold for thermal and mechanical stimuli in mice Increased nerve conduction velocity, the number of intraepidermal nerve fibers, myelin thickness, and axonal Diameters	1007
	Rat BMSCs	Exosomes	–	MDA, HIF1α, NOX2, Caspase 3, BAX, PARP1, MPO, ICAM1, IL-1β, NF-κB ↓ SOD, CAT, GPX, HO-1, BCL2, IL-10, bFGF, HGF, SOX9, VEGF ↑	Decreased histopathological score of kidney injury in rats Reduced the levels of blood urea nitrogen (BUN) and Creatinine Reduced the level of oxidative stress Increased antioxidant status Reduced apoptosis and inflammation Improved regeneration and enhanced angiogenesis	1008
	Human endometrial MSCs	Exosomes	–	Tie2, VEGF, Ang1, Ang2 ↑	Increased the expression of angiogenesis markers, including Tie2, VEGF, Ang1, and Ang2, and increased the proliferation, migration, and angiogenesis of HUVECs	1009

TABLE 32 (Continued)

Phase	Exosome source	Nomenclature	Related exosomal cargo	Secreted factors or expressed genes affected	Outcome	References
	Human umbilical cord mesenchymal stem cells (hUC-MSCs)	Exosomes	–	Ang2 ↑	huc-MSC-Ex-derived Ang-2 plays a significant role in tube formation of HUVECs and promotion of angiogenesis	1010
	Human UC blood-MSCs	Exosomes	–	Ang, Ang1, HFG, VEGF ↑	Human umbilical cord blood (UCB)-MSC-derived exosomes pretreated with thrombin could accelerate skin wound healing in rats with full-thickness wounds. Exosomes from human UCB-MSCs increased angiogenesis factors, such as VEGF, HGF, and Ang1, and decreased TNF-α and IL-6	1011
	Human UC-MSCs	Exosomes	Wnt4	β-catenin, N-cadherin, PCNA, Cyclin D3 ↑	Enhanced angiogenesis in rats through the Wnt4/β-catenin pathway. When the expression of Wnt4 was knocked out by shRNA, the pro-angiogenic effect of hUC-MSC-derived exosomes was eliminated	114
	Human UC-MSCs	Exosomes	–	α-SMA, collagen I ↓	Increased the formation and maturation of new blood vessels at the wound site, although the mechanism is still unclear	784
	Human UC-MSCs	Exosomes	GSK3β-Wnt/β-catenin	–	Alleviated hepatic IRI by transporting miR-1246 via regulating GSK3β-mediated Wnt/β-catenin pathway	1012
Remodeling Phase	Human gingival MSCs	Exosomes	–	Collagen ↑	Reduced the formation of scars by inhibiting the accumulation of mouse myofibroblasts	1013
	Adipose mesenchymal stem cells (ASCs)	Exosomes	–	N-cadherin, cyclin-1, PCNA collagen I, III ↑	Facilitates cutaneous wound healing via optimizing the characteristics of fibroblasts	779
	ASCs	Exosomes	ERK/MAPK	Matrix metalloproteinases-3 (MMP3) ↑	A promoted ECM reconstruction in cutaneous wound repair by regulating the ratios of collagen type III: type I, TGF-β3:TGF-β1, and MMP3:TIMP1, and by regulating fibroblast differentiation to mitigate scar formation	999
	MenSCs	Exosomes	–	iNOS ↓ ARG1, VEGF ↑	Resolved inflammation and ameliorated cutaneous non-healing wounds in diabetic mice Induced M2 macrophage polarization	720

Note: Reprinted with permission from Zeng and Liu.[995]

Abbreviations: AIF, apoptosis-inducing factor; Ang, angiopoietin; ASC, human adipose mesenchymal stem cell; BMMSC, bone marrow MSC; BMSC, bone marrow-derived stem cells; CTGF, connective tissue growth factor; DLL4, delta-like 4; ECM, extracellular matrix; EGF, Epidermal growth factor; EVs, extracellular vesicles; FD, human fetal dermis; FGFs, fibroblast growth factors; HaCaTs, human keratinocytes; hBM, human bone marrow; HDFs, human dermal fibroblasts; HGF, hepatocyte growth factor; hUC, human umbilical cord; HUVECs, human umbilical vein endothelial cells; IFNs, interferons; IGF-1, insulin growth factor 1; IL, interleukin; ILVs, intraluminal vesicles; iNOS, inducible nitric oxide synthase; iPSC, induced pluripotent stem cell; JMMSC, jaw bone marrow MSC; KGFs, keratinocyte growth factors; LPS, lipopolysaccharide; MMP, matrix metalloproteinases; MSCs, mesenchymal stem cells; MVBs, multivesicular bodies; NAP-2, neutrophil activating peptide-2; PDGF, Platelet-derived growth factor; PF-4, Platelet factor 4; ROS, reactive oxygen species; SDF-1α, stromal-cell-derived factor-1; TGF-β, Transforming growth factor; TIMP1, tissue inhibitor of metalloproteinase 1; TNF-a, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

wounds, burn healing, and post-irradiation (Table 33).[994] A study by An et al.[987] demonstrated that exosomes improved healing via the following four mechanisms:

- Control of inflammation and immune system
- Encouraging wound angiogenesis
- Accelerating the growth and regeneration of skin cells
- Controlling the process of collagen remodeling to prevent excessive scar formation

In summary, previous studies have revealed that exosomes had a positive impact on fat grafting, diabetic ulcer wound healing, scarless wound healing, and could effectively be utilized in conjunction with carriers such as hydrogels or fibrin (Figure 30).[987] Figure 31 summarizes how exosomes assist during cutaneous wound healing.

6.5 | Dermatology and skin regeneration

Much like the effects of exosomes on cutaneous wound healing, there are many benefits to utilizing MSC-Exos for dermatological conditions. Their ability to be utilized for skin healing has been popularized not only in medicine but also in the field of facial esthetics since it encompasses a multi-billion-dollar industry where specific exosomes for dermatological conditions (Dermasomes) have been utilized for skin health and antiaging benefits.

6.5.1 | Atopic dermatitis

Often referred to as atopic eczema, atopic dermatitis (AD) is a common inflammatory skin condition marked by persistent, uncontrollably high inflammatory reactions.[1024] About 8% of adults and 20% of children have been diagnosed with the condition.[1025] Unfortunately, it remains unknown what exact molecular pathway leads to the pathogenesis of the illness. Major pruritus and erythematous lesions are the disease's primary symptoms having a major negative impact on a patient's quality of life.[1024] Pharmacological intervention, such as corticosteroids and calcineurin inhibitors, is the mainstay of therapy for AD. A number of negative side effects as well as the development of drug resistance have been reported. As a result, several investigators have stated that the development of novel, more potent, and less hazardous treatments is critically needed in this field. MSCs have been useful in AD healing, much like in the repair of chronic wounds.[1024] MSC-Exos provide a stronger treatment option for AD as they are more stable and have less immunogenicity than the cells from which they are isolated, yet they perform the same biological tasks.[1026] This circumvents the majority of issues related to live MSC-based treatment options.

In recent years, greater Th2 cytokine levels have been primarily linked to increased vulnerability to AD (inside-outside theory).[186,1026,1027] Because of this, the majority of research has focused on lowering Th2-mediated immune responses. However, current research has shown a clear link between aberrant gene expression-driven epidermal barrier defects and immune response dysregulation, such as increased Th2 cytokine levels. Cho et al. showed that human ADSC-Exos may provide a potential cell-free therapeutic approach for the treatment of AD.[183] In an in vivo animal model, researchers found that ADSC-Exos reduced the production of various inflammatory cytokines, including IL-4, IL-23, IL-31, and TNF-alpha. In an oxazolone-induced dermatitis model, Shin et al. found that subcutaneous ASC-exosome injection substantially decreased TSLP, IL-5, IL-13, TNF-, IFN-, and IL-17.[186]

6.5.2 | Psoriasis

The most prevalent chronic inflammatory skin condition, psoriasis, affects around 125 million individuals globally.[1028] Impaired keratinocyte differentiation and proliferation are linked to the condition. Furthermore, it has been observed that the immune system cells massively invade troubled areas.[1029] It manifests as red squamous plaques that are restricted to the head, elbows, knees, and sacroiliac area.[1028] Unfortunately, the exact cause of psoriasis is still unknown. However, past studies indicate that the condition is influenced by T cells and dendritic cells. The immunology of the disease has been well explained by Lowes et al.[1030] EVs have a role in the pathophysiology of psoriasis, just as they do in AD.[1029] Research is still being done on the use of EVs as therapeutic agents to control psoriasis. On the other hand, Zhang and colleagues reported encouraging results using exosomes produced from human umbilical cord mesenchymal stem cells (huc-MSCs-Exo).[1031] Injection of huc-MSCs-Exo subcutaneously decreased the levels of IL-17, IL-23, CCL20, and STAT3/p-STAT3. Additionally, exosomes inhibited the maturation activation of dendric cells and prevented IL-17's positive impact on keratinocytes.[1031]

6.5.3 | Medical esthetics

People are now more than ever more conscious of their physical appearance. Consequently, self-esteem is often affected by apparent skin aging processes, scars, or hair loss. This has spurred the growth of aesthetic medicine, which is continuously looking for novel, minimally invasive, and highly successful cosmetic interventions. Increased research on exosome use for skin rejuvenation, scar removal, and hair loss has been spurred by promising results with exosomes in regenerative medicine (discussed later in this section). In a study titled: "Stem cell-derived exosomes: A groundbreaking development in cosmetic dermatology," Shen et al. discovered that exosomes produced from stem cells play a critical role in several aspects of skin cosmetology, including wound healing, skin aging, and scar formation.[1032] Today many commercial entities exist selling dermal exosomes (aka Dermasomes).

TABLE 33 Studies that evaluated an in vivo role for MSC-EVs in wound healing.

Study	EV source	Model	Findings
Fang et al.[784]	Human UC-MSC	Mouse skin wound • Local injection	EVs reduced scar formation and myofibroblast accumulation
		In vitro dermal fibroblasts	EVs suppressed TGF-β induced myofibroblast formation. EVs were enriched in miR-21, miR-23a, miR-125b, and miR-145. miRNA delivery reduced TGF-β/SMAD2 signaling in fibroblasts
Hu et al.[779]	Human AD-MSC	Mouse skin wound • Local injection	EVs improved rate of wound healing, increased Col1 and Col3 mRNA on Day 3 and Day 5 post wounding, and decreased Col1 and Col3 mRNA on Days 7 and 14
		Mouse skin wound • Intravenous injection	EVs migrated to wound site (Days 5–14) and spleen and promoted wound healing
		In vitro fibroblasts	EVs promoted fibroblast proliferation and migration, increased mRNA for N-cadherin, COL1, COL3, and elastin
Zhang et al.[1014]	Human AD-MSC	Mouse skin wound • Local injection	EVs improved rate of wound healing, decreased scar size, and neoangiogenesis
		In vitro fibroblasts	EVs promoted fibroblast proliferation and migration, and increased mRNA for COL1, COL3, MMP1, FGF2, and TGF-β1. Fibroblasts had increased p-AKT. Application of PI3K/AKT inhibitor Ly294002 abrogated the EV-induced effects on fibroblasts
He et al.[998]	Human BMSC	Mouse skin wound • Intravenous injection	EVs promoted wound healing and polarization of macrophages to M2 phenotype
		In vitro human monocytes/macrophages	EVs promoted M2 macrophage polarization in part through transfer of miR-223
Ren et al.[1015]	Human AD-MSC	Mouse skin wound • Local injection	EVs accelerated wound healing, re-epithelialization, collagen deposition, and neovascularization
		In vitro fibroblasts, keratinocytes (HaCaT), and endothelial cells (HUVEC)	EVs promoted proliferation and migration, and stimulated AKT and ERK signaling
Cheng et al.[1016]	Human UC-MSC	Mouse skin wound • Local injection	EVs accelerated re-epithelialization and promoted collagen fiber maturation
		In vitro dermal fibroblasts and keratinocytes (HaCaT)	EVs promoted proliferation and migration. The effect was blocked by miR-27b inhibitor. Proposed miR-27b acts by suppressing ITCH, thereby activating JUNB/IRE1α
Jiang et al.[1017]	Human BMSC	Mouse skin wound • Local injection	EVs from MSCs with TSG-6 overexpression (TSG-6-EVs) and knock-down (TSG-6-KD-EVs). EVs reduced scar formation, reduced production of TGF-β1, Collagen I and III, and α-SMA protein, and suppressed SMAD2/3 signaling. TSG-6-EVs enhanced the effect of EVs, the effect was lost in TSG-6-KD-EVs, and when TSG-6 neutralizing antibodies were present
Liu et al.[1018]	Mouse BMSC	Mouse skin wound • Topical in pluronic F127 hydrogel	Topical EVs accelerated wound healing, limited inflammatory infiltrate, and decreased scar size
		In vitro mouse macrophages	EVs polarized macrophages toward M2 phenotype. Conditioned media from EV treated macrophages promoted fibroblast proliferation and migration

TABLE 33 (Continued)

Study	EV source	Model	Findings
Qiu et al.[1019]	Mouse BMSC	Mouse skin wound • Local injection	EVs from MSCs treated with EVs from neonatal serum and adult serum. MSC-EVs accelerated wound healing and promoted neoangiogenesis. Neonatal serum stimulated MSC-EVs showed more robust effect
		In vitro endothelial cells (HUVECs)	MSC-EVs promoted HUVEC proliferation, migration, and tube formation, and increased p-AKT and p-eNOS. Neonatal serum stimulated MSC-EVs showed more robust effect
Zhang et al.[1004]	Human AD-MSC	Mouse skin wound • Local injection	EVs promoted mouse wound healing, proposed to occur in AKT/HIF-1α dependent fashion
		In vitro HaCaT keratinocytes	EVs promoted HaCaT keratinocyte proliferation
Zhao et al.[1005]	Human UC-MSC	Mouse skin wound • Local injection	EVs enhanced re-epithelialization and neoangiogenesis
		In vitro keratinocytes (HaCaT)	EVs stimulated keratinocyte proliferation, migration, and suppressed ROS induced apoptosis. Proposed effect was through suppression of AIF nuclear translocation and PARP-1 activation
Li et al.[1020]	Human AD-MSC	In vitro human hypertrophic scar fibroblasts	EVs decreased collagen deposition, transdifferentiation of fibroblasts-to-myofibroblasts, and formation of hypertrophic scar. EVs were noted to express miR-192-5p, which can suppress IL-17RA/SMAD axis
Diabetic wounds			
Wang et al.[721]	Mouse AD-MSC	Mouse diabetic wound • Topical in complex hydrogel (Pluronic F127, oxidative hyaluronic acid, and Poly-L-lysine)	EVs improved wound healing and neovascularization. The effect was improved when EVs were loaded in complex hydrogel
Li et al.[714]	Mouse BMSC	Mouse diabetic wound • Local injection	EVs from MSCs overexpressing lncRNA H19 (H19-EVs). Only H19-EVs promoted wound healing, decreased inflammatory infiltrate, and increased granulation tissue formation
		In vitro human fibroblasts from diabetic foot ulcers and health control	H19-EVs reduced miR-152-3p expression in fibroblasts from diabetics and increased PTEN expression
Shi et al.[723]	Mouse AD-MSC	Mouse diabetic wound • Local injection	EVs accelerated wound healing, increased angiogenesis, suppressed apoptosis, and increased autophagy markers SIRT1 and LC3. The effects were further enhanced with EVs from mmu_circ_0000250 overexpressing MSCs
		In vitro endothelial cells (HUVECs)	EVs promoted HUVEC survival under high glucose conditions and increased autophagy. This was enhanced by loading with mmu_circ_0000250, which was shown to increase SIRT1 mediated autophagy
Yang et al.[726]	Human UC-MSC	Mouse diabetic wound • Topical in Pluronic F127 hydrogel	EVs accelerated wound healing and angiogenesis, increased expression of VEGF and TGF-β1

(Continues)

TABLE 33 (Continued)

Study	EV source	Model	Findings
Pomatto et al.[1021]	Human BMSC AD-MSC	Mouse diabetic wound • Topical in carboxymethylcellulose	AD-MSC-EVs, but not BMSC-EVs, promoted the rate of wound healing. Comparative in vivo analysis of scar and angiogenesis was not performed
		In vitro fibroblasts, keratinocytes, and endothelial cells	BMSC-EVs promoted proliferation of keratinocytes and endothelial cells, and promoted viability of fibroblasts, keratinocytes, and endothelial cells. AD-MSC-EVs promoted only the proliferation of endothelial cells. Protein and miRNA analysis indicated BMSC-EVs are enriched for proliferative factors, whereas AD-MSC-EVs are enriched in pro-angiogenic factors
Ti et al.[128]	Human UC-MSC	Rat diabetic wound • Local injection	EVs from LPS preconditioned MSCs (LPS Pre-EVs) decreased inflammatory cell infiltration and polarized macrophages toward M2
		In vitro human monocytes (THP-1)	LPS Pre-EVs induced M2 polarization. EVs transferred Let-7b, reducing TLR-4 expression and NF-kB activation
Li et al.[718]	Human AD-MSC	Rat diabetic wound	EVs from MSCs overexpressing NRF2 (NRF2-EVs). Endothelial progenitor cells (EPC) + NRF2-EVs promoted wound healing better than EPC + AD-MSC-EVs, and both were better than EPC alone or control
		In vitro human epithelial progenitor cells (EPC)	EVs decreased EPC senescence under high glucose conditions. NRF2-EVs inhibited inflammatory cytokines and ROS
Ding et al.[710]	Human BMSC	Rat diabetic wound • Local injection	EVs from deferoxamine stimulated MSCs (DFO-EVs). EVs promoted wound healing and neoangiogenesis, and DFO-EVs were more effective
		In vitro endothelial cells (HUVECs)	DFO-EVs were more potent stimulators of HUVEC proliferation and tube formation than EVs. DFO-EVs proposed to transfer miR-126 to HUVECs, which suppresses PTEN, and thereby activates AKT signaling
Liu et al.[724]	Human BMSC	Rat diabetic wound • Local injection	EVs from MSCs treated with melatonin (MT-EVs). EVs promoted wound closure, Collagen I and III expression, and M2 macrophage polarization; MT-EVs enhanced the effect of EVs
		In vitro mouse macrophages (RAW264.7)	MT-EVs were more potent than EVs at polarizing macrophages to M2 phenotype
Yu et al.[725]	Human BMSC	Rat diabetic wound • Local injection	EVs from MSCs treated with atorvastatin (ATV-EVs). EVs promoted wound healing and angiogenesis. ATV-EVs were more effective
		In vitro endothelial cells (HUVECs)	EVs promoted proliferation, migration, and tube formation, increased VEGF secretion, and activated AKT/eNOS signaling. ATV-EVs produce a larger magnitude effect compared to standard EVs. ATV-EVs proposed to work by upregulating miR-221-3p in endothelial cells
Burn wounds			
Shafei et al.[711]	Human AD-MSC	Mouse burn wound • Topical in alginate hydrogel	EVs accelerated wound closure, increased epithelial thickness, collagen deposition, and neovascularization

TABLE 33 (Continued)

Study	EV source	Model	Findings
Zhang et al.[1022]	Human iPSC-MSC	Rat burn wound • Local injection	EVs accelerated re-epithelialization, reduced scar width, promoted collagen maturation, and stimulated neoangiogenesis. Effects depended on EV transfer of Wnt4
		In vitro fibroblasts and endothelial cells (HUVECs)	EVs stimulated proliferation and migration, stimulated Collagen I and III, and elastin secretion, and promoted tube formation
Li et al.[135]	Human UC-MSC	Rat burn wound • Intravenous injection	EVs reduce inflammation following burn wounds. EVs transfer miR-181c and reduce TLR4 signaling
		In vitro mouse macrophages (RAW264.7)	EVs suppress LPS-induced macrophage inflammation

Note: Reprinted with permission from Bray et al.[992]

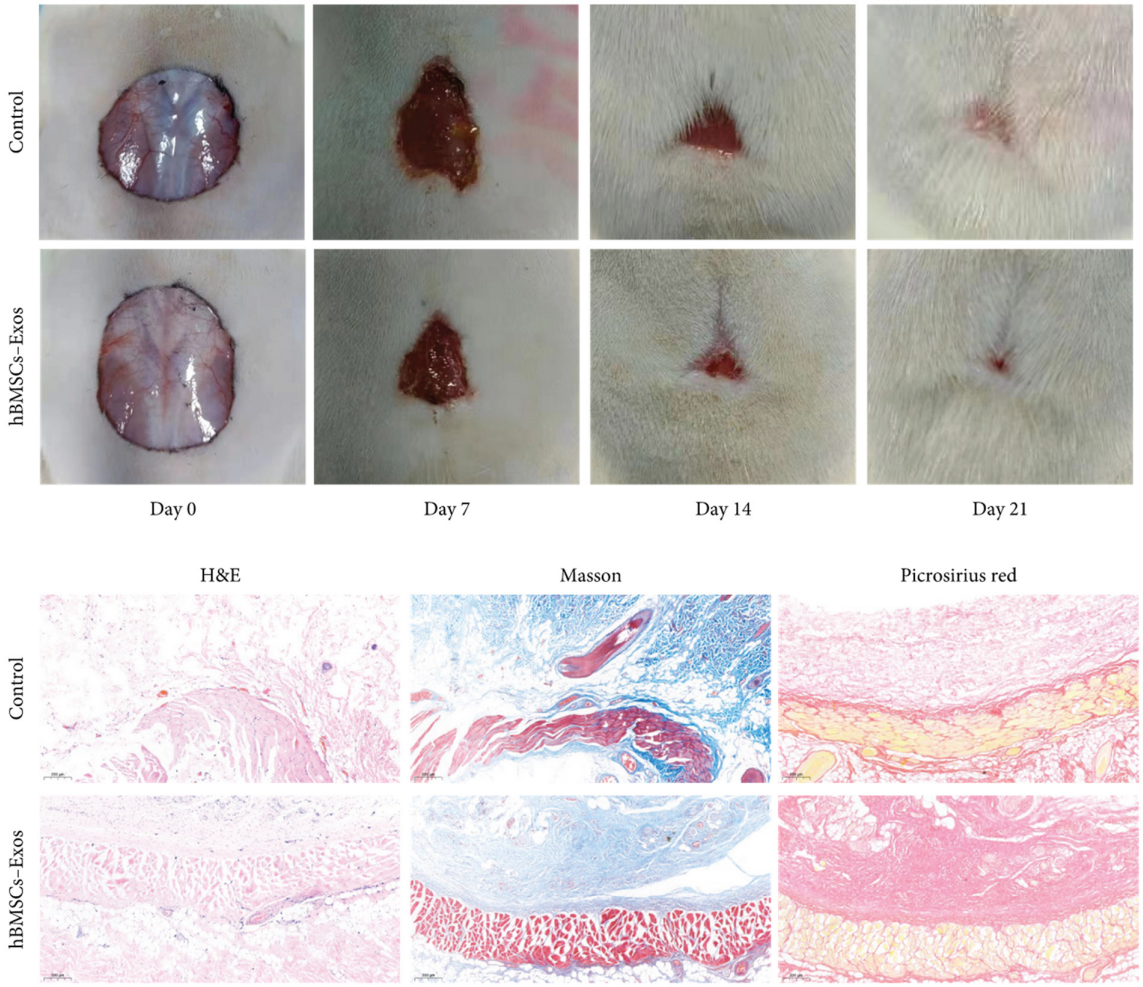

FIGURE 30 Representative photographs shown of full-thickness excision wound area of the rat treated with PBS (control) or hBMSCs-Exos. Reprinted with permission from Jiang et al.[1000]

6.5.4 | Potential capacity of stem cell-derived exosomes in skin aging

Aging skin is caused by both external and internal factors. Age dependency and natural aging are referred to as intrinsic aging, which is influenced by genes, while external aging, sometimes referred to as photoaging, is caused by environmental variables.[1033] UVB light is the most powerful environmental element that causes skin photoaging. Cell damage is caused by ultraviolet B induced DNA mutations and oxidative stress.[1034,1035]

The ECM and dermal fibroblast activity are important factors of youthful skin. Studies show that reductions in collagen type I and III

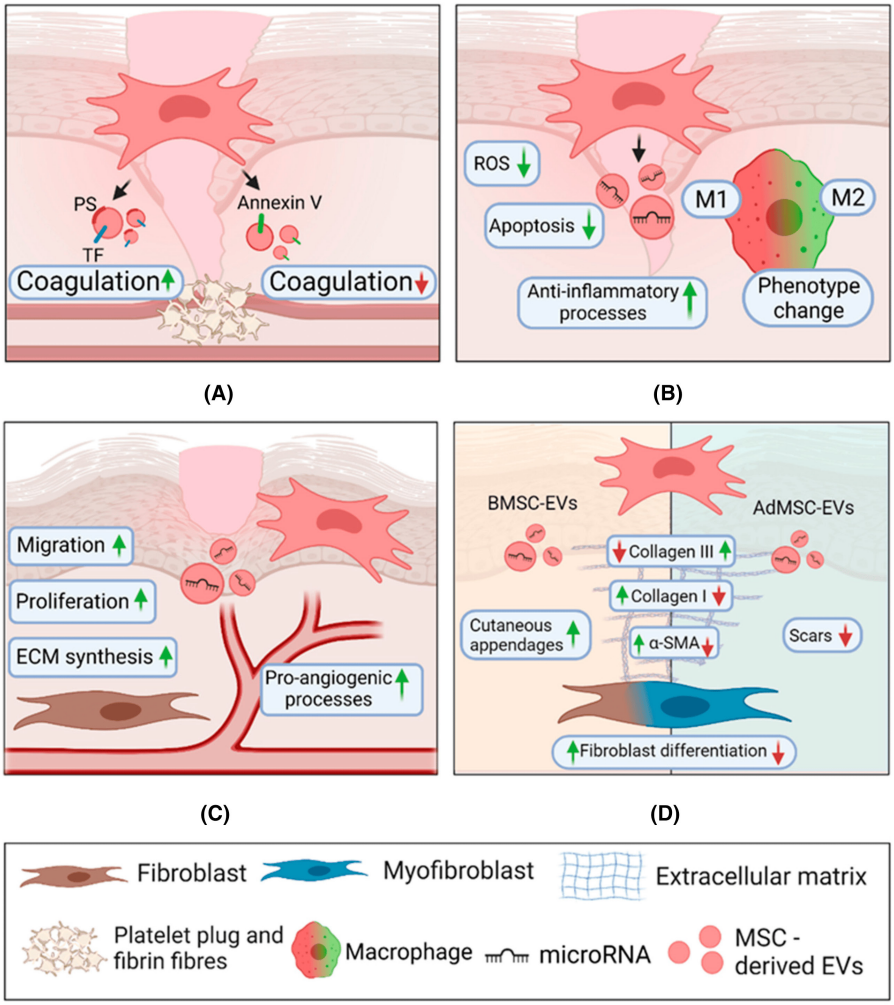

FIGURE 31 Role of mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) in wound healing. (A) MSC-EVs in hemostasis. MSC-EVs contain pro- and anticoagulant factors, which balance and regulate blood coagulation. (B) MSC-EVs in inflammation. MSC-EVs support anti-inflammatory processes, reducing reactive oxygen species (ROS) synthesis, alleviating apoptosis, and inducing macrophage phenotype change from pro-inflammatory (M1) to anti-inflammatory (M2). (C) MSC-EVs in proliferation. MSC-EVs stimulate fibroblast migration and proliferation to the wound site, resulting in raised levels of extracellular matrix (ECM) components synthesis. Also, MSC-EVs can promote vascularization. (D) MSC-EVs in remodeling. Bone marrow MSC-EVs (BMSC-EVs) increase collagen I production, smooth muscle actin (SMA) and fibroblast differentiation to myofibroblast; however, they decrease collagen III synthesis. Besides, BMSC-EVs boost new cutaneous appendage formation. Adipose mesenchymal stem cell extracellular vesicles (AdMSC-EVs) act opposite and lead to scar reduction. Reprinted with permission from Narauskaite et al.[1023]

synthesis and fragmentation of collagen fibrils define the molecular structure of aged skin.[1036] One of the most significant ECM proteins that provides tissues a younger, more full appearance is collagen. The key to skin elasticity is elastin.[1037] But as fibroblasts age, their capacity to proliferate and synthesize collagen is diminished.[1038] Furthermore, the elevated production of matrix metalloenzymes expedites the degradation of collagen, ultimately resulting in the formation of wrinkles and other visible signs of skin aging.[1034] Numerous researchers have shown that MSC-Exos play a significant role in mitigating skin aging and deterioration.[1039]

Exosomes have been shown to have a greater impact on fibroblast senescence than other constituents.[901] Exosomes produced from human-induced pluripotent stem cells (iPSCs), for instance, have the ability to prevent HDFS from aging. iPSCs-Exos have the ability to control the amount of MMP-1/3 and enhance the production of type I collagen in senescent HDFS.[1034] MMP-1, functioning as a collagenase, participates in the production of a secretase enzyme that breaks down interstitial collagens I, II, and III.[1040] Multiple studies have shown a correlation between the increase in fibroblast growth and the activation of collagen production, which is influenced by the presence of TGF-β and PDGF.[1034,1041] Previous studies have shown that human dermal fibroblasts take up MSC-Exos and stimulate cell migration and synthesis of skin collagen I and elastin.[1042] Zhang and colleagues showed that exosomes produced from ADSCs enhanced fibroblasts' levels of type I and type III collagen and accelerated wound healing via the PI3K/Akt signaling pathway.[1014] These investigations demonstrate that stem cell-derived exosomes have significant potential use in postponing the aging of the skin by stimulating the production of collagen. Figure 32 highlights some benefits of exosomes on skin healing.

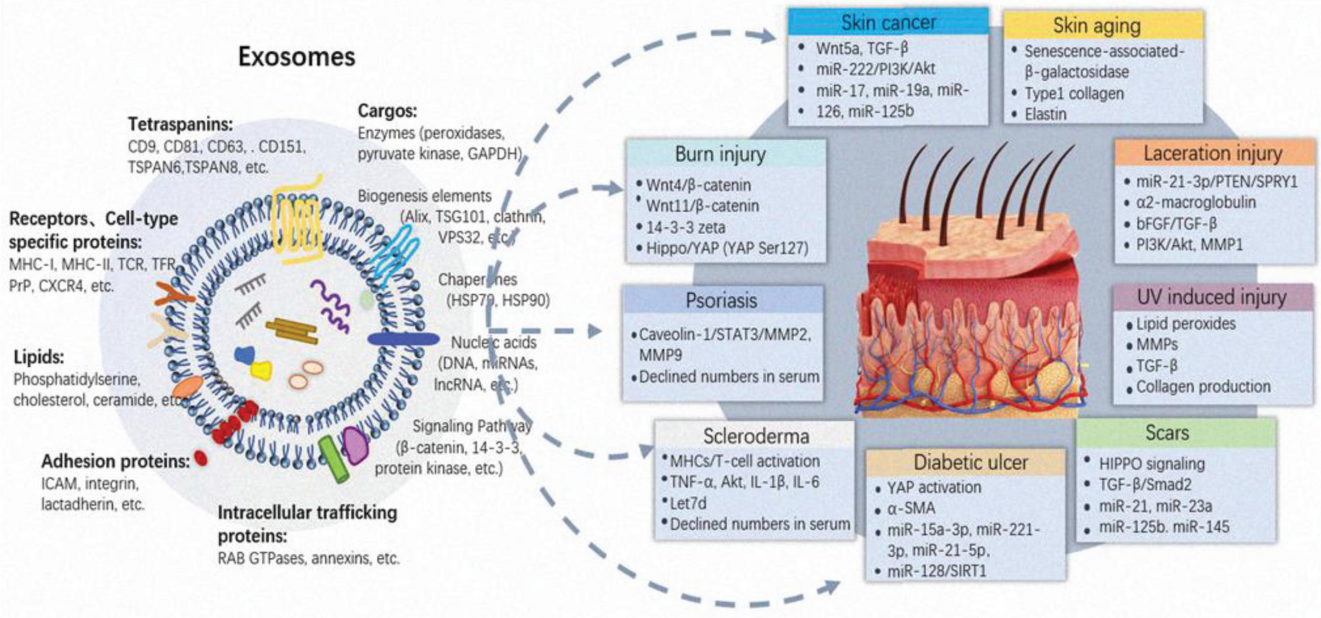

FIGURE 32 Main composition of exosomes and their functions on skin injuries. Despite the different origin and mode of biogenesis, exosomes display a similar appearance, and common composition. Exosomes are featured by tetraspanins, receptors or cell-type specific proteins, lipids, adherin proteins, intracellular trafficking proteins. Deep analysis of extracellular vesicle composition reveals that they convey various cargoes, including nucleic acids, proteins (biogenesis elements, chaperones, and signaling pathway molecules) and lipids, which all vary widely between cells and conditions. The vast information will directly affect the fate and function of exosomes in skin injuries. Exosomes participate in multiple cutaneous diseases including laceration, burn, aging, diabetic wound healing, scar formation, skin autoimmune disease, and skin cancers, through different biological pathways. Reprinted with permission from Shi et al.[1043]

6.5.5 | Stem cell-derived exosomes in repair, regeneration, and angiogenesis

Inflammation, hyperplasia, and remodeling are all part of the intricate and dynamic process of skin wound healing. Type M2 polarization of macrophages regulates inflammation. Exosomes released by human mesenchymal stem cells are capable of lowering neutrophil counts and preventing the recruitment of macrophages during the inflammatory phase. Therefore, exosomes from human MSCs may lessen the inflammatory response and are crucial for skin repair and regeneration during the proliferative stage because they encourage fibroblast migration, proliferation, and endothelial cell creation.[114] Bin and colleagues found that huc-MSC exosomes activate the Wnt4/β-catenin signaling pathway to promote endothelial cell migration, proliferation, and formation.[114] Huc-MSC-Exos also promoted β-catenin nuclear translocation and activity via the Wnt4 pathway, hence increasing fibroblast migration and proliferation.[1002] Jieyuan discovered that the angiogenic activities of endothelial cells might be facilitated by exosomes released from endothelial progenitor cells via the Erk1/2 signaling pathway, ultimately stimulating cutaneous wound healing and regeneration.[1044]

Exosomes generated from human umbilical cord blood (UCB-Exos) have been shown to inhibit phosphatase and tensin homolog (PTEN) and sprout homolog 1 (Spry1), hence promoting wound healing and reducing scarring. These effects could be connected to UCB-Exos high expression of miR-21-3p.[1045] Exosomes produced from menstrual blood-derived mesenchymal stem cells were shown by Dalirfardouei to promote neoangiogenesis via VEGF. Accordingly, the acceleration of epithelial regeneration in mice was directly linked to the overexpression of the NF-κB p65 subunit and the activation of the NF-κB signaling pathway.[720] These findings imply that exosomal treatment created from stem cells could be a potential therapeutic strategy and that administering stem cell-derived exosomes may improve endothelial cells' angiogenic potential, fibroblast migration, and proliferation.

6.5.6 | Potential capacity of stem cell-derived exosomes in reduced scar formation

Scar development takes place mostly during the wound remodeling period. Early gestation fetuses are observably capable of scarless wound healing as compared to adult wounds.[999] The ultimate objective of cosmetic dermatology is to achieve scarless recovery. Scarless tissue differs from scar tissue in many ways. It is characterized by the presence of fine reticular collagen, a lower degree of crosslinking, less inflammation, and a reduced number of myofibroblasts. The ratios of TGF-β3 to TGF-β1, type III to type I collagen, and MMPs to matrix metalloproteinase tissue inhibitors (TIMPs) were all greater in scar-free tissue.[999]

Activated fibroblasts replace the injured epithelial or endothelial cells during the process of tissue regeneration and repair after injury.

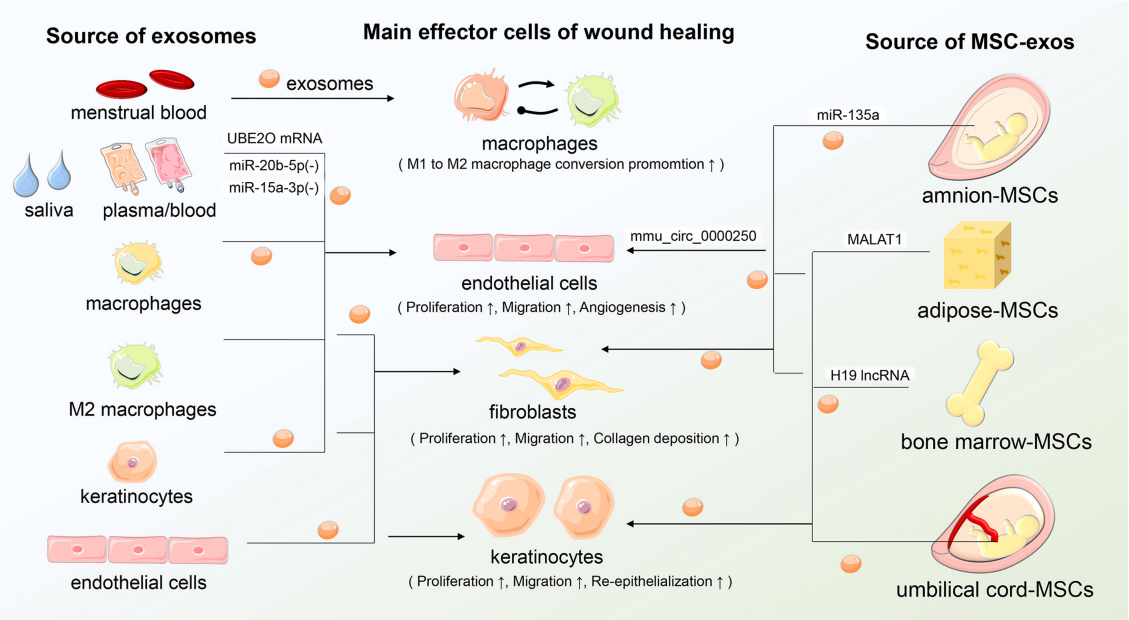

FIGURE 33 Exosomes derived from multiple sources could regulate wound healing by affecting effector cells. The exosomes from various sources, including MSCs, keratinocytes, endothelial cells, immune cells, and body fluid, could regulate the wound healing process through different mechanisms. Especially, the UBE2O mRNA in saliva-exos, the miR-135a in amnion-derived MSC-exos, the MALAT1 and mmu_circ_0000250 in adipose-derived MSC-exos, and the H19 lncRNA in bone marrow-derived MSC-exos played positive roles in enhancing the functions of main effector skin cells to accelerate wound healing. The miR-20b-5p in exosomes of patients plasma and miR-15a-3p in exosomes from patients blood inversely impaired the functionality of the endothelial cells, exerting healing delay effects. Mesenchymal Stem Cells, MSCs. Reprinted with permission from Xiong et al.[1049]

Fibroblasts have the capacity to overproduce fibronectin, hyaluronic acid, type I and III collagens, and other ECM components, which may result in scarring and matrix overgrowth.[1046] Exosomes have been shown in several studies to have a significant role in preventing the development of scars (Figure 33).[720,1047]

During wound healing, HDFs develop into myofibroblasts. Following wound healing, a significant fraction of myofibroblasts undergo apoptosis. Myofibroblasts, however, are still active and multiplying in hypertrophic scar patients.[1048] Research has shown that human ADSC-Exos have the ability to control the ratios of TGF-β3 and collagen type III to type I: TGF-β1, MMP3, and TIMP-1 by inhibiting fibroblast development into myofibroblasts.[999]

Chen et al.[1048] demonstrated that by preventing the function of miR-200C3p in fibroblasts, lncRNAasLNCS5088 from M2 macrophage exosomes may contribute to the development of scars. This provides evidence that exosomes may facilitate intercellular communication in the management of hyperplasia in scarring.[1048] Therefore, stem cell-derived exosomes have shown to be a successful noninvasive scar reduction therapy. Nevertheless, further studies are required to fully understand how stem cell-derived exosomes contribute to the reduction of scars.[999,1017]

6.6 | Dental regeneration

A number of systematic reviews have now investigated the use of exosomes for the treatment of various dental tissues.[1050-1060] In fact, part 3 of this 3-part series is dedicated entirely to the use of exosomes in dentistry. In that systematic review, a total of 944 articles were identified using exosomes in the dental field for either their regenerative/therapeutic potential or for diagnostic purposes derived from salivary exosomes. In total, 113 research articles were selected for their regenerative potential (102 in vitro, 60 in vivo, and 49 studies were both). Therapeutic exosomes were most commonly derived from dental pulps, periodontal ligament cells, gingival fibroblasts, stem cells from exfoliated deciduous teeth, and the apical papilla have all been shown to facilitate the regeneration of a number of tissues including bone, cementum, the periodontal ligament, nerves, orthodontic tooth movement, and temporomandibular joint disorders, among others. Results demonstrate that the use of exosomes led to positive outcomes in 100% of studies. In the bone field, exosomes were found to perform equally as well or better than rhBMP2. Periodontitis animal models were treated with simple gingival injections, and benefits were even observed when the exosomes were administered intravenously. Exosomes are much more stable than growth factors commonly utilized in the dental space and, as such, were shown to be far more resistant to degradation by periodontal pathogens found routinely in a periodontitis environment. Comparative studies in the field of periodontal regeneration found better outcomes for exosomes even when compared to their native parent stem cells. In total, 47 diagnostic studies have revealed a role for salivary/crevicular fluid exosomes in the diagnosis of birth defects, cardiovascular disease, diabetes, gingival recession detection, gingivitis, irritable bowel syndrome, neurodegenerative disease, oral

lichen planus, oral squamous cell carcinoma, oro-pharyngeal cancer detection, orthodontic root resorption, pancreatic cancer, periodontitis, peri-implantitis, Sjögren syndrome, and various systemic diseases. Hence, dental exosomes (Periosomes) were described as possessing "remarkable" potential, serving as a valuable tool with significant advantages for dental clinicians.

6.7 | Erectile dysfunction

A study by Khodamoradi et al. 2022 titled: "Exosomes as Potential Biomarkers for Erectile Dysfunction, Varicocele, and Testicular Injury", examined the possibility of using exosomes as biomarkers for a number of ailments, including erectile dysfunction.[1061] It was determined that exosomes are a viable therapeutic method since they may contain cargo such as specific medications and therapeutic compounds. As discussed earlier (Section 5.1.8), erectile dysfunction is a blood flow issue which is the reasoning behind its association with diabetes specifically as well as other noncommunicable diseases such as smoking, cardiovascular diseases, and obesity.[701] Therefore, the use of exosomes in the treatment of arterial inflow or venous outflow problems will undoubtedly have a positive effect concerning erectile dysfunction. Additionally, exosome therapy for several male sexual and reproductive diseases has been tested in a number of clinical trials.[1061] Gaining insight into the significant function of exosomes in the reproductive system may provide new opportunities for developing novel treatment approaches and diagnostic markers.[1062] This may be a promising method for managing conditions including testicular damage, varicocele, and erectile dysfunction.[1061]

6.8 | Hair regrowth

Alopecia is a prominent reason for seeking dermatological consultations. However, the management of this condition continues to be challenging. Androgenic alopecia is the predominant cause of non-scarring hair loss, which affects around 80% of Caucasian men and 50% of women by the age of 70. On the other hand, central centrifugal cicatricial alopecia is the leading cause of hair loss among African Americans.[1063] Patients with alopecia have severe psychological effects.[1063]

Because alopecia is so common, a lot of research has been done with the aim of developing safe and efficient therapies. Topical minoxidil and oral/topical finasteride are two FDA-approved therapies that may partially stop hair loss but not fully stimulate hair growth. Additionally, side effects and difficulty sticking to regular treatment regimens may further restrict the usage of these drugs.[1063] Although low-level laser treatment has FDA approval as well, its effectiveness is unknown.[1064] Patients may be able to have surgical therapy via hair transplantation, but the expense may prevent them from doing so.[1064] Therefore, current research is focused on regenerative therapies that not only stop hair loss but also encourage growth. In many clinical trials, platelet-rich plasma injection therapy (PRP), a minimally invasive treatment, has been shown to improve hair density and volume.[1065]

In a study titled: "Exosome Therapy in Hair Regeneration: A Survey of the Literature on the evidence, difficulties, and prospects for the future", Kost et al. thoroughly examined the exosomes' capacity for regenerative hair growth.[1063] Exosome therapies have been shown in preclinical trials to have distinct advantages in regenerative medicine and hair loss therapy. Clinical investigations support the safety of using exosomes in medicine, although there is a shortage of information regarding the effectiveness and safety of exosome treatment for alopecia.[1063]

The majority of preclinical data supporting the use of exosomes in alopecia comes from exosomes produced by dermal papilla cells (DPCs), a collection of specialized mesenchymal cells found at the base of hair follicles (HFs).[1066] They have been shown to be essential for controlling the creation, development, and cycling of HF.[1067] Studies in mice have demonstrated that injecting DPC exosomes accelerates the start of HF anagen while slowing down HF catagen. Immunohistochemistry studies revealed elevated amounts of β-catenin and Sonic Hedgehog (Shh) in the treated skin, which control the hair cycle, as well as H&E-stained tissue sections revealing anagen VI phase in the treated animals. Treatment of outer root sheath cells with DPC exosomes further confirmed the overexpression of β-catenin and Shh10 in vitro. There is evidence that DPC-exosome therapy enhances the migration and proliferation of cells found in the outer root sheath, namely those cells found in the hair follicle bulge.[1067] Similar to what Kwack et al. found when they subcutaneously gave DPC exosomes to mice, exosomes have been shown to promote protracted anagen of hair follicles.[1068] Research in mice with alopecia areata suggests that DPC exosomes may reduce inflammation in hair follicles and stop hair loss.[1069]

In addition, DPCs are critical for HF stem cell differentiation. Epithelial cells near the follicular base die during catagen and telogen, but the DP stays alive and moves up to the HF bulge. There, it releases signals that initiate the anagen phase by stimulating the differentiation of HF stem cells and regenerating HFs.[1070] Yan et al. showed that the co-culture of HF stem cells with DPCs stimulated HF stem cell development. Additionally, transmission electron microscopy observation revealed that DPC exosomes were adhered to the surface of HFSCs during co-culture.[1071] Ultimately, they found that 111 miRNAs were expressed differently in DPC exosomes than in DPCs, suggesting that DPC exosomes are important for HF regeneration.[1071] It is worth mentioning that DPC exosomes have demonstrated the ability to influence ADSCs, causing their transformation into DPC-like cells that produce genes related to hair growth, such as β-Catenin and hair-inducing miRNAs.[1072]

There are a number of other exosome sources known to exist for hair growth treatment. In vitro, the maintenance of hair human dermal papilla cells was shown using exosomes derived from hair outer root sheath cells.[1073] Furthermore, compared to a control

group, exosomes from the outer root sheath increased markers of hair growth induction by a ratio of 2.1, 1.7, and 1.3, respectively.[1073]

Lastly, exosomes produced by immune cells have also shown potential in the therapy of alopecia. In a mouse model of alopecia areata, exosomes from myeloid-derived suppressor cells, which inhibit T cell growth, increased FoxP3 and arginase 1 levels to prevent T-cell hyperreactivity.[1074] Additionally, in a mouse model and in vitro studies using human hair follicles, macrophage exosomes have shown noticeably higher amounts of hair-inductive indicators of DPCs.[1075] It has also been shown that exosomes produced by the bacterium Leuconostoc holzapfelii, which was isolated from human scalp tissue, regulate hair development via the Wnt/β-catenin signal transduction pathway.[1076]

Zhou et al.[1067] found that in mice models, DP cell exosomes derived from healthy human scalp specimens sped up the beginning of anagen and postponed catagen, leading to higher levels of β-catenin and Shh. Accordingly, human dermal papillae exposed to activated human dermal fibroblasts (hDFs) release the non-Wnt ligand Norrin via stimulated extracellular vesicles (st-EVs).[1077] Frizzled-4 (Fzd4), the particular receptor for Norrin given by hDF, is thought to promote the β-catenin pathway's subsequent activation, which leads to the observed increased hair follicle development ex vivo (Figure 34).[1077]

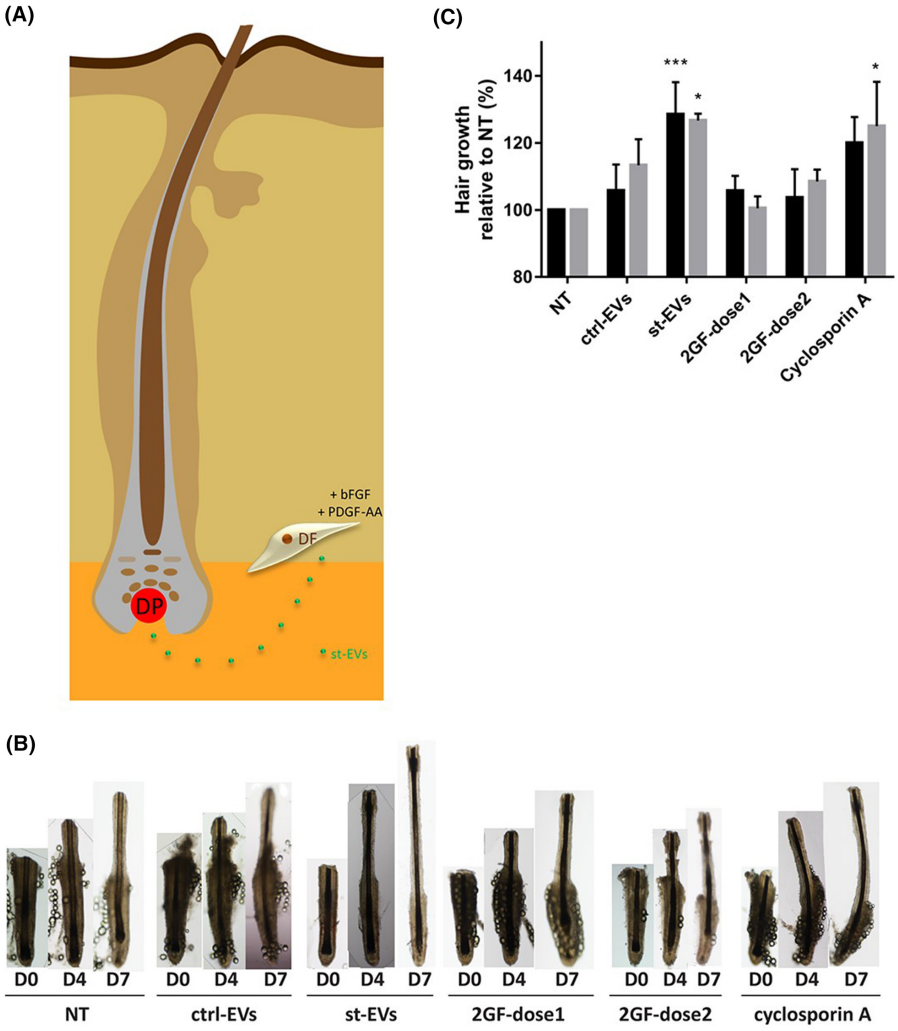

FIGURE 34 St-EVs improve human hair growth. (A) Schematic representation of DP cell treatment by EVs isolated from DF stimulated by 2GFs. (B) Individual HFs were dissected from adult human scalp tissue and placed in culture in the presence of PBS (nontreated [NT]), cyclosporin A (10^{-7} M), ctrl-EVs, or st-EVs (5×10^9 particles per milliliter) and two different concentrations of bFGF and PDGF-AA named 2GF-dose1 and 2GF-dose2 at D0 and D4. Pictures of follicles were taken at three points (D0, D4, and D7) and the length of each follicle was measured over time. (C) Quantification of the length of hair fibers overtime relative to NT. Data represent experiments performed on different donors at Days 4 and 7 following HF extraction (D4/D7): NT, ctrl-EVs, st-EVs, and cyclosporin A were obtained from four donors at D4 and three donors at D7; 2GF-dose1 and 2GF-dose2 were obtained from three donors at D4 and two donors at D7 and are expressed as mean ± SD. $^*p < 0.05$ and $^{***}p < 0.001$ compared with NT HFs using one-way analysis of variance followed by Dunnett's multiple comparison test for D4 and Kruskal–Wallis test followed by Dunn's multiple comparison test for D7. 2GF, two growth factors; bFGF, basic fibroblast growth factor; D0/4/7, Day 0/4/7; DF, dermal fibroblast; DP, dermal papilla; EVs, extracellular vesicles; HF, hair follicle; PDGF-AA, platelet-derived-growth factor A; st-EVs, EVs from stimulated DF. Reprinted with permission from Riche et al.[1077]

When combined, research indicates that exosomes from different tissue sources may be very advantageous for hair regeneration and rejuvenation inside the HF dermal papilla, outer root sheath, and HF bulge cells.

6.9 | Spinal cord injury and intervertebral disc repair

A potentially fatal and catastrophic lesion to the spinal cord, spinal cord injury (SCI) results in either temporary or permanent alterations to the cord and partial or whole loss of motor, sensory, and autonomic functioning.[1078,1079] SCI commonly results in paralysis, sometimes known as quadriplegia or paraplegia, with sensory impairment occurring below the site of the damage.[1080] In most cases, it causes patients and healthcare systems to bear very heavy psychological and financial costs.[1081,1082] It also has adverse effects on most fundamental body processes, including breathing, the operation of the bowel and bladder, hormone production, and sexual function. This is because the peripheral nerve system and brain are no longer connected.[1083] The prevalence and incidence of SCI are estimated to be 236–4187 per million persons globally, with up to 770000 new cases annually. Males under the age of 30 are more likely to have SCI than females.[1084–1086]

The first mechanical insult, which may be produced by physical forces including contusion, compression, transection, or stretching of the spinal column, often leading to disruption of the spinal cord and results in primary damage.[1087–1091] An instantaneous mechanical damage to the spinal cord is referred to as a primary injury since it is an irreversible procedure.[1092,1093] A series of secondary injuries follow the initial damage, worsening the spinal cord's health.[1094,1095] Secondary injury occurs shortly after the initial mechanical injury and is characterized by local vascular damage, ionic changes, thrombosis, edema, ischemia, progressive hemorrhage, oxidative stress caused by the release of free radicals, lipid peroxidation, excitotoxicity, and cell death facilitated by apoptosis and cell necrosis.[1079] Moreover, the inflammatory response and excessive growth of glial cells, which occur after the subsequent suppressive environment and scar tissue, impede the regrowth of nerve fibers and restrict the effectiveness of treatment.[1096,1097]

Recovery from SCI remains significantly restricted, even though recent therapeutic advancements in SCI care have shown some improvement in patients' quality of life.[1098,1099] For the purpose of treating SCI, three main groups of pathologic targets may be distinguished. First, at the site of the original trauma, surgical decompression, and the removal of mechanical spinal cord compressing material.[1079,1100–1104] Second, anti-inflammatory therapies for the area around the damaged spinal cord.[1105–1107]

Third, the ultimate objective for treating spinal cord injuries is axonal regrowth at the location of the damage.[1083] Following the initial SCI, the damaged lesion is heavily invaded by macrophages, which help to create a cavity of injury (COI) surrounding the site of injury, stopping neuronal regrowth.[1108–1111] Scarring interferes with axonal regrowth,[1112] and the COI lesions that were filled with fluid prevent axons from traversing the liquid-filled COI without the aid of bridge-like structures.[1113] Furthermore, granulomatous infiltration surrounding the injured spinal cord, known as arachnoiditis, aids in the development of a mature scar devoid of astrocytes or other glial cells.[1097] Patients with SCI continue to have a dismal prognosis, a high death rate, and a noticeably shorter life expectancy.[1114] Figure 35 highlights the phases of injury.[1115]

Astrocytes are crucial to the process of SCI because they may either impede or facilitate the central nervous system's (CNS) recovery.[1116–1120] A1 and A2 reactive astrocyte phenotypes are

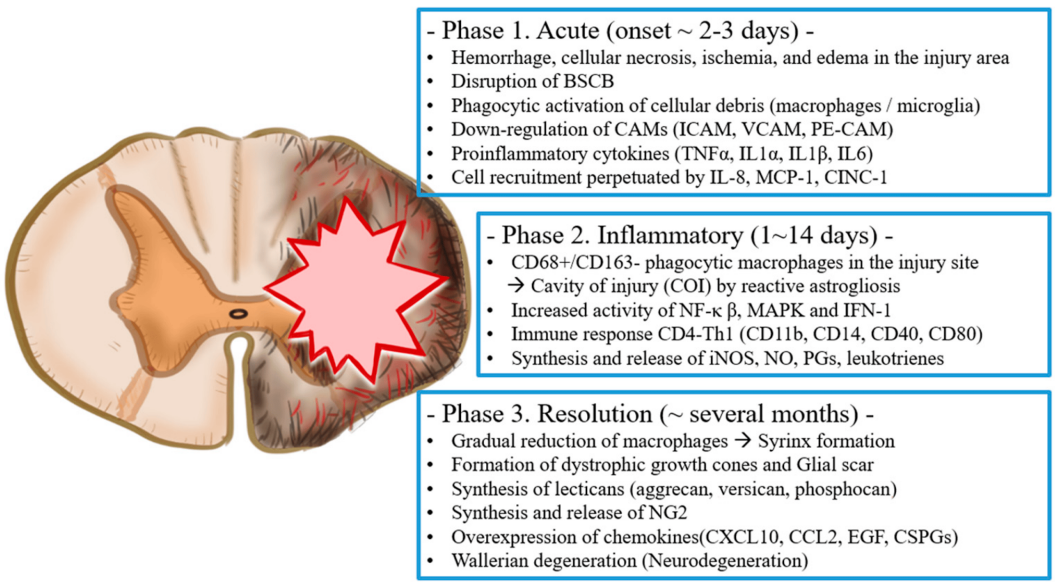

FIGURE 35 Schematic diagram for damage stages and responses in spinal cord injury. Reprinted with permission from Kim et al. 2021.[1080]

pre-existing and are brought on by ischemia and neuroinflammation. A1 astrocytes may cause neuronal and oligodendrocyte death because of their neurotoxic effects on myelin, synapses, and neurons. They are often generated just after SCI that is triggered by IL-1, TNF-alpha, and C1q.[1121] On the other hand, by upregulating the production of certain neurotrophic factors, A2 astrocytes provide a protective effect.[1116] As a result, one possible therapeutic option for SCI might be selective suppression of A1 astrocytes. Moreover, it has recently been shown that red blood cells (RBCs) around SCI lesions are eliminated by reactive astrocytes via phagocytosis. This process, known as astrocytic erythrophagocytosis, is thought to aid in the quick evacuation of dispersed RBCs from the area of injury to stop macrophage aggregation and the ensuing harmful inflammation. MicroRNAs (miRNAs) have been implicated in tissue damage and regeneration processes in recent times, and several miRNAs have garnered interest as possible targets for the treatment of SCI.

6.9.1 | Regenerative potential of stem cell-derived extracellular vesicles in spinal cord injury

Spinal cord injury is a severe ailment that is progressive and very difficult to treat, requiring urgent medical treatment owing to its intricate pathophysiology and impact on social status and financial load. A paper published recently by Herbert et al.[1122] found that the mechanism of action of exosomes on spinal cord injury involves at least eight processes including (1) tissue sparing and neuroprotection, (2) alleviation of oxidative stress, (3) induction and progression of angiogenesis, (4) pericyte role restoring integrity of the blood–spinal cord barrier, (5) combating endoplasmic reticulum stress, (6) modulation of inflammatory response, (7) activation of autophagy, and (8) attenuation of apoptosis. Interestingly, animal studies have demonstrated significant benefit when utilized typically within 1 hour of injury but also following subsequent IV infusions up to 21 days (Tables 34 and 35). Noteworthy, protocols could be developed within an early time frame for athletes playing contact sports such as rugby or American football, where the likelihood of injury is more significant. Protocols have been proposed and are in development to improve patient outcomes following trauma. Figure 36 highlights the benefits of exosomes in SCI.

6.9.2 | Use of exosomes in intervertebral disc degeneration

In today's world, low back pain (LBP) is a common health issue that has serious socioeconomic ramifications.[1157,1158] According to epidemiological data, 80% of individuals will, at some point in their lives, have lower back discomfort.[1159] LBP is thought to be one of the main factors limiting the amount of labor that individuals under 45 may be capable of.[1160,1161] In the United States, the direct cost of treating LBP is estimated to be over 30 billion US dollars, while the indirect socioeconomic losses are estimated to be around 100 billion US dollars.[1162]

Previous studies[1162–1165] found that the most common cause of LBP currently is IVD. Despite the fact that the exact cause of IVD is still unknown, age, metabolic diseases, mechanical stress, trauma, illness, diet, and genetic susceptibility are some of the contributing variables.[211,1160]

Currently, bed rest, the use of nonsteroidal anti-inflammatory medicines (NSAIDs) and other analgesics, lumbar discectomy, and interbody fusion are the major clinical treatments for LBP.[1162] Nevertheless, these methods just concentrate on providing temporary relief for the symptoms rather than directly addressing the underlying cause, resulting in the inability to halt or stop the advancement of IVDD.[212,1166] Hence, innovative therapeutic approaches are required for the treatment of IVDD. Recently, therapies based on MSCs and exosomes derived from MSCs have shown promising benefits and may have practical applications.[1165,1167–1170]

Noor et al.[1171] found that exosomes produced from MSCs not only have an essential function in tissue repair and regeneration but also possess a longer-lasting, more powerful, and easier-to-maintain role when compared to parent cells. While the use of MSC-Exos in IVD therapy is still in its infancy, there is rising interest in this approach. An increase in oxidative stress, decreased ECM content, inflammation, and cell death are the pathophysiological characteristics of IVD. Targeting these four aspects of the illness, MSC-Exos may help to improve all symptoms related to IVD. The results of previous research on IVD regeneration and repair utilizing exosomes produced from MSCs are compiled in Table 36. In 2022, research by Lu et al.[1172] compiled 16 research studies and discovered that MSC-Exos were obtained from various cell sources for the treatment of IVD. These sources included human-induced pluripotent stem cells (1 study), unspecified tissues (2 studies), BMSCs (10 studies), ADSCs (1 study), umbilical cord MSCs (1 study), and placenta-MSCs (1 study). In a preclinical model of IVD, MSC-Exos exhibited comparable therapeutic benefits despite variable tissue sources.[1172] These effects are primarily attributed to the restoration of extracellular matrix integrity, promotion of cell proliferation, reduction of cell death, regulation of inflammatory response, and attenuation of oxidative stress.[1172]

6.10 | Vascular regeneration

Several pathologies affecting the vasculature, particularly the microvasculature, lead to a lack of physiological homeostasis control of patency and adequate perfusion to meet tissue metabolic needs. Most diseases involving failing organs and tissues include microvascular dysfunction as an essential underlying component. Vascular decreased angiogenic potential density, endothelial dysfunction, ER stress, mitochondrial dysfunction, oxidative stress, increased senescence, and apoptosis are pathogenic variables that contribute to this dysfunction.[1188–1190]

TABLE 34 Mechanistic overview of EV therapy and molecular outcomes in SCI.

Route of administration	Window period	Therapeutic intervention	Dose	TF/cytokines/signaling pathway	Outcome	References
Tail vein	1 h	BMMSC exosome	100 μg	↓ C3, C4b, C6, C5, Mbl, Cfp, C1q and Cfh ↓ p-p65 (NF-κB) and p-IκBα	↓ Complement system activation and inflammation	1123
Tail vein	1 h and day 7	hUCB MSC-derived Nano-Vesicle	25 μg	↓ TNFα, Il1b, Nos2 ↑ **Arg1, Il10, and VEGF**	M1 → M2 neuroprotection, anti-inflammation, angiogenesis	1124
Tail vein	Every 3 days till 27 days	BMMSC exosome	200 μg	↓ Bax, Cleave caspase-3 ↑ **Wnt/b-catenin** ↑ **Bcl-2, caspase-3** ↑ **LEF-1 and TCF-1**	↓Neuronal apoptosis ↑Motor recovery	1125
Tail vein	Immediate	NSC-EV-14-3-3t	200 μg	↓ Cleave caspase-3, TNF-α, IL-1β and IL-6 ↑ **Bcl-2**	↓ Apoptosis, inflammation ↑ Autophagy	1126
Tail vein	Immediate	UCB-CD34$^+$ CM	–	↓ GFAP, IL-1b, TNF-a, and MPO ↑ **IL-10**	↓ Oxidative stress, inflammation, astrogliosis	1127
Lumbar cistern	24 h	Subventricular zone-derived EV	1 μg	↓ TNF-α IL-1β, IL-18, and IL-6	Motor function recovery and ↓ inflammation	1128
Tail vein	30 min	BM MSC exosome	40 μg	↓ C3 and GFAP TNF-α, IL-1α, and IL-1β, p-IKBα and nuclear p65	↓ A1 astrocyte, inflammation, apoptosis	1129
Tail vein	Immediate	GIT1-overexpressing BMMSC exosome	200 μg	↑ **PI3K/AKT** ↑ **CS56** ↓ TNF-a, IL-1b and IL-6	↓ Inflammation, Apoptosis and glial scarring	1130
Tail vein	Immediate	Epidural fat (EF)-mesenchymal stem cells (MSCs)	–	↓ NLRP3, ASC, and active-caspase-1, IL-1β, IL-18, and TNF-α	↓ Inflammation, expression of activated microglia	1131
Intra thecal	1 day	"Neuro cells" (HSC, MSC)	100 μL	↓GFAP	↓Astrogliosis	1132
Tail vein	1 day	BMMSC EV	200 μL EV (200 μg/mL)	↓NF-kB	↓ Pericyte migration ↑ Integrity of the BSCB	1133
Tail vein	Immediate	NSC-derived exosomes	100 μg	–	↓ Apoptosis ↑ Nerve regeneration	1134
Tail vein	-	MSC miR-21 and miR-19b exosome	–	↓ PTEN	↓ Apoptosis	1135
Tail vein	1 h	BMMSC exosome	100 μg	↓ FasL gene	↓ Apoptosis	1136
			200 μg	–	↑ Autophagy	1137
			100 μg	↓ IL-1a, TNF-a, and IL-17B and IL-36b	↓ Inflammation	1138

(Continues)

TABLE 34 (Continued)

Route of administration	Window period	Therapeutic intervention	Dose	TF/cytokines/signaling pathway	Outcome	References
Tail vein	24 h	BMMSC mir133b exosome	100 μg	↑ **GAP43, pERK1/2, CREB and STAT3**	↑ Axonal outgrowth	1139
Intrathecal	Week 1,2,3	hWJMSC CM	–	↑ **GAP43** ↓ Irf5, Mrc1 Il1b, TNFα	↓ Glial scar ↑Axonal outgrowth	1140
Scaffold implantation	Immediate	hMSC exosomes	–	↓GFAP ↓iNOS	↓Astrogliosis ↓Inflammation	1141
Tail vein	Immediate	Bone MSC miR-216a-5p exosome	200 μg	↑ **Arg1, CD206, YM1/2, PI3K/AKT (↓ TLR4/ NF-κB)**	↓Inflammation Functional recovery	1142
Tail vein	1 h	BM MSC CM	30 μg (15×10^9 EV	↓IL-1β	Improved spatial learning impairments ↓ Inflammation	1143
Tail vein	1 h	BMSC-miRNA-29b exosome	100 μg	↑ **GAP-43, NF200**	Neuronal regeneration	1144
In vitro	–	BMSC CM	100 μM	↓ Notch1, Hes1 Bax, Cleave caspase-3 ↑ **Bcl-2, caspase-3**	↓ Oxidative stress and apoptosis	1145
Tail vein	30 min	hUC-MSC exosome	200 μg	↓ iNOS, TNF-α, IL-6, IFN-γ, G-CSF, MCP-1, and MIP-1α, ↑ **IL-10, IL-4**	Macrophage polarization M1 → M2 ↓ Inflammation	1146
Tail vein	30 min	MSC miR-126 exosome	100 μg (1×10^{10})	↓ SPRED1 and PIK3R2 ↓ Bax, Cleave caspase-3 ↑ **Bcl-2** ↑ **VEGF**	↑ Angiogenesis ↑ Neurogenesis ↓ Apoptosis	1147

Note: Exosomes exert their therapeutic potentials in SCI through the regulation of various molecular mechanisms. The administration, therapeutic window period, route, and dosage are vital players determining the extent of functional recovery. There is dynamic regulation of molecules, crosstalk between pathways, and homeostasis involved in the outcomes to contain the secondary injury that is the key for functional recovery in SCI (↑ – Upregulation, ↓ – downregulation). Reprinted with permission from Herbert et al.[1122]

Abbreviations: ANGPT1, angiopoietin; Arg1, arginase 1; ASC, apoptosis-associated Speck-like protein; BDNF, brain-derived neurotrophic factor; bFGF, fibroblast growth factor; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GM-CSF, granulocyte macrophage colony-stimulating factor; HGF, hepatocyte growth factor; HLA-G, human leukocyte antigen-G; HSC, hematopoietic stem cell; hUCBMSC, human umbilical cord blood-derived mesenchymal stem cell; hUC-MSC, human umbilical cord mesenchymal stem cell; Iba-1, ionized calcium binding adaptor molecule 1; IGF-1, insulin-like growth factor; IL10, interleukin 10; IL-10, interleukin 10; IL4, interleukin 10; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; iPSC, induced pluripotent stem cell; lncRNA, long non-coding RNA; MBP, myelin basic protein; MCP-1, monocyte chemoattractant protein-1; miRNA, microRNA; MSC, mesenchymal stromal cells; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; PGE-2, prostaglandin E2; PIGF, phosphatidylinositol-glycan biosynthesis class F protein; PIK3R2, phosphoinositide-3-kinase regulatory subunit 2; PKA, protein kinase cAMP-dependent; PPAR-γ, peroxisome proliferator-activated receptor gamma; SOD, superoxide dismutase; SPRED, sprouty-related EVH1 domain-containing protein 1; TGF-β, transforming growth factor beta; TLR4, Toll-like receptor 4; VASH, vasohibin 1; VEGF, vascular endothelial growth factor.

TABLE 35 List of publications on EVs' therapeutic effect in SCI.

EVs sources	Routes	Models	↑ Score	Proposed mechanisms
Rat BMSC	iv	Contusion	4.5 at Week 4	Anti-apoptosis, anti-inflammation, pro-angiogenesis[1149]
Rat BMSC	iv	Contusion	4.5 at Week 4	neuroprotection, reduce A1 astrocytes, anti-inflammation, anti-apoptosis[1129]
Rat BMSC	iv	Contusion	3 at Week 4	Anti-microglia and A1 neurotoxic reactive astrocytes, anti-inflammation, anti-apoptosis, reduce scar, pro-angiogenesis[1150]
Rat BMSC	iv	Hemisection	3 at Week 4	Inhibit complement activation[1123]
Rat BMSC	iv	Contusion	2 at Week 4	Anti-apoptosis[1125]
Rat BMSC	iv	Hemisection	6 at Week 4	Anti-apoptosis[1136]
Rat BMSC	iv	Contusion	6 at Week 4	Inhibit pericyte migration, decrease BSCB permeability[1133]
Rat BMSC (miR-133b-enriched)	iv	Compression	3 at Week 2	Decrease RhoA expression, axon growth[1139]
Rat BMSC (miR-29b-enriched)	iv	Contusion	11 at Week 8	Neuroprotection[1144]
Rat BMSC (miR-126-enriched)	iv	Contusion	7 at Week 4	Anti-apoptosis, pro-neurogenesis, pro-angiogenesis[1147]
Rat BMSC (hypoxic)	iv	Contusion	4 at Week 4	Macrophage polarization[1142]
Human BMSC	iv	Contusion	3 at Week 2	Decreases reactive microglia and astrocytes[1151]
Human UC-MSC	iv	Contusion	2 at Week 8	Macrophage polarization, anti-inflammation[1146]
Human adipose-MSC	iv	Contusion	5 at Week 4	Attenuate NLRP3 inflammasome activation[1131]
Rat-NSC	it	Compression	6 at Week 4	Anti-inflammation[1128]
Rat-NSC	it	Contusion	7 at Week 4	Inhibit NLRP3 inflammasome complex formation[1152]
Rat-NSC (14-3-3t-enriched)	iv	Contusion	4 at Week 4	Enhance autophagy, anti-apoptosis, anti-inflammation[1153]
Rat-NSC (IFG-1-stimulated)	iv	Contusion	5 at Week 4	Anti-apoptosis, anti-inflammation[1134]
Mouse NSC	iv	Contusion	4 at Week 4	Activate autophagy, anti-apoptosis, anti-inflammation, anti-microglia[1126]
Mouse pericytes	iv	Contusion	3 at Week 2	Improve microcirculation, protect BSCB, anti-apoptosis[1154]
Human BMSC (PTEN siRNA)	in	Full transection	7.5 at Week 8	Anti-inflammation, anti-scarring, pro-angiogenesis, axon growth[1155]

Note: Reprinted with permission from Guo et al.[1148]

Abbreviations: ↑ Score, increased mean BBB or BMS locomotor score from EVs treatment groups, compared to untreated controls; BM, bone marrow; BSCB, blood–spinal cord barrier; in, intranasal; it, intrathecal; iv, intravenous; MSC, mesenchymal stem/stromal cells; NSC, neural stem cells; UC, umbilical cord.

Many therapeutic settings now use pharmacologic treatments that focus on a limited aspect to alleviate symptoms of pathology rather than adopting a complete strategy to tackle the underlying cause. In response to this issue, much attention has been directed to cellular treatments and cell-free therapies, such as exosomes, which can address the complex causes of vascular and microvascular dysfunction.[1188]

Furthermore, Kawasaki disease, antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, giant cell arteritis, Behçet's disease, and other multisystem autoimmune diseases are included in the diverse group of multisystem autoimmune disorders known as systemic vasculitis.[1191,1192] Thrombosis, vascular stenosis/occlusion, aneurysm development, or bleeding are frequent complications of vasculitis, which is defined by inflammation in specific-sized arteries.[1193] Patients continue to face issues like early death, recurrence, co-morbidities, and a lower quality of life. Despite advances in earlier diagnosis and novel immunotherapies in recent decades,[1194] the therapeutic potential of exosomes has attracted increased attention, and studies in this area are ongoing.[1195]

7 | INFECTIOUS DISEASES

It is interesting to note that exosomes have been effectively used to treat a variety of infectious disorders. Exosomes were first used to treat infectious disorders like hepatitis in an effort to replace tissues

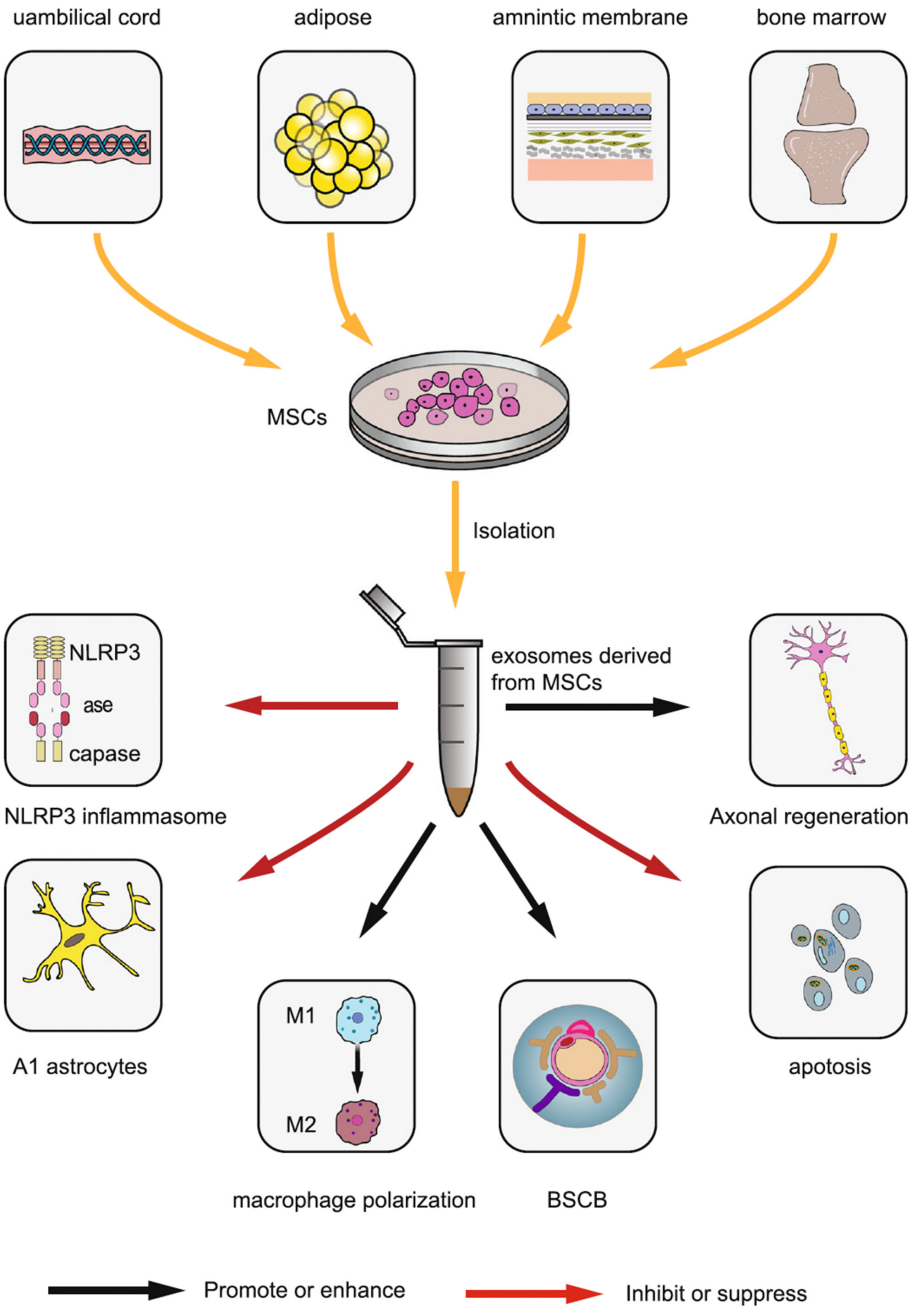

FIGURE 36 Therapeutic effects of exosomes derived from different MSCs in the treatment of SCI. MSCs can be obtained from bone marrow, the umbilical cord, the amniotic membrane, and adipose tissue. Exosomes derived from MSCs have anti-inflammatory and anti-apoptotic effects, as well as inhibit A1 astrocytes, promote axonal regeneration and macrophage polarization, and protect the BSCB from spinal cord injury. Reprinted with permission from Liu et al.[1156]

and organs that the viruses had damaged.[1196] Globally, morbidity and mortality have been significantly attributed to infectious illnesses; pneumonia and respiratory infections are among the leading causes of death globally.[1197] Finding novel therapeutic approaches to fight infections and repair organ and tissue damage caused by infections is essential given the rising frequency of infectious disease outbreaks and the lack of efficient therapies.[1198]

Coronavirus disease 2019 or COVID-19 was one of the leading clinical uses of exosomes where numerous clinical trials were started to minimize the 'cytokine storm' leading to many injuries/deaths. The global impact of the COVID-19 pandemic may be attributed to the emergence of a new virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belonging to the coronavirus family. This infectious agent has affected a significant number of individuals on a global scale.[1199,1200] Acute respiratory distress syndrome (ARDS) brought on by COVID-19 dramatically raises death rates in patients who are older or have chronic illnesses such as diabetes, heart, lung, or kidney problems. No effective treatment

TABLE 36 Preclinical studies investigating the therapeutic potential of stem cell-derived exosomes on IVDD.

Study	Cell type	Species of cell source	Size of EV	Isolation	Model	Modeling method	In vitro appraisement	In vivo appraisement	Additional manipulation
Qi et al.[1173]	UC MSC	Human	–	Ultra-centrifugation	In vitro	–	• MSC exosome has the potential to alleviate HG induced extracellular matrix degradation via the p38 MAPK pathway • HG also significantly inhibited collagen II and aggrecan expression in NPMSCs, and leads to an increase in the rate of NPMSCs apoptosis • miRNAs array results and bioinformatics analysis predicted that miR-221-3p, let-7a-5p, and miR-21-5p derived from hUC-MSCs-EXO may be closely related to extracellular matrix synthesis of NPMSCs	–	High glucose (HG) induced degradation of IVD
Li et al.[1174]	BM MSCs	Human	Around 100 nm	Ultra-centrifugation	In vitro	–	• In the pathological acid environment, MSC-derived exosome promotes the expression of chondrocyte extracellular matrix, collagen II, and aggrecan, and reduces matrix degradation by downregulating matrix-degrading enzymes • MSC-derived exosomes were able to prevent and mitigate NPC apoptosis through repressing caspase—3 expression and attenuating caspase-3 cleavage induced by acidic pH	–	Acidic pH-induced NPCs apoptosis
Li et al.[1175]	BM MSCs	Human	Around 100 nm	Ultra-centrifugation	In vitro	–	• BMSC-derived exosomes inhibit IL-1b-induced inflammation and apoptosis of AF cells by suppressing PI3K/AKT/mTOR signaling pathway-mediated autophagy • BMSC exosomes supported AF cell viability after IL1-β treatment	–	IL1-β treatment (10 ng mL^{-1})
Yuan et al.[1176]	PLMSCs	Human	30–150 nm	Ultra-centrifugation	In vitro In vivo	–	• MSC exosomes riched in antagomir-4450 ameliorates NPC damage by promoting proliferation and migration • EV-derived AntagomiR-4450 decreased MMP13, IL6, IL1-β, CASP3 expression, and increased COL2 and ACAN expression 3. miR-4450 was significantly upregulated while ZNF121 was downregulated in IDD and miR-4450 exacerbated NPC damage by targeting ZNF121	• The EXO-antagomiR-4450 attenuated IVDD damage by repressing miR-4450 and upregulating ZNF121 expression • The EXO-antagomiR-4450 could partially decline the pro-inflammatory factors and MMPs in IDD mice	TNF-α (10 ng mL^{-1}) treatment

(Continues)

TABLE 36 (Continued)

Study	Cell type	Species of cell source	Size of EV	Isolation	Model	Modeling method	In vitro appraisement	In vivo appraisement	Additional manipulation
Zhu et al.[1177]	BMMSCs	Rat	Mainly 109.3 nm	Ultra-centrifugation	In vitro	–	• MSC exosomes could inhibit TNF-α-induced increase of apoptotic process, activation of apoptotic proteins, imbalance of anabolism/catabolism levels, and accumulation of collagen I in NPc through the delivery of miR-532-5p • RASSF5 is a direct target gene of miR-532-5p to mediate the cell apoptosis regulation	–	TNF-α (20 ng mL^{-1}) treatment
Wen et al.[1178]	BMMSCs	Rat	About 80 nm	Ultra-centrifugation	In vitro In vivo	Injection of absolute ethanol into sub-endplate in rat tail to induce IVD degeneration	• The expression of col II and Aggrecan, SA-β gal positive cells and apoptosis rate of NPCs were decreased after MSC exosomes intervention • Reducing miR-199a carried by MSC exosomes led to an impaired protective effect of exosomes on NPCs • miR-199a from MSC exosomes promotes repair by targeting GREM1 and downregulating the TGF-β pathway	• After MSCs-exosomes treatment, MMP-2, MMP-6, TIMP1 and TUNEL-positive cells were decreased, and miR-199a was increased in IDD mice • BMSCs-EVs promote proliferation of NPCs and inhibit apoptosis	–
Zhu et al.[1179]	BMMSCs	Mouse	80 nm	Ultra-centrifugation	In vitro	–	• MSCs exosomes alleviated NPCs apoptosis by reducing IL-1β-induced inflammatory cytokines secretion and MAPK signaling activation • MSCs exosomes inhibited NPCs apoptosis and MAPK signaling by delivering miR-142-3p that targets mixed lineage kinase 3 (MLK3)	–	IL1-β treatment (10 ng mL^{-1})
Cheng et al.[1180]	BMMSCs	Human	Average 87 nm	Ultra-centrifugation	In vitro In vivo	The model of disc degeneration was established by needle puncture (needle-stab model)	• MSC exosomes were taken up by NPCs and suppressed NPC apoptosis induced by TNF-a • miR-21 in MSC exosomes alleviated TNF-a induced NPC apoptosis • Delivery of miR-21 in MSC exosomes inhibited NPC apoptosis by targeting PTEN through PI3K-Akt pathway	• Intradiscal injection of MSC exosomes alleviated the NPC apoptosis and IVD degeneration in a rat model	TNF-α (5 ng mL^{-1}) treatment
Zhang et al.[1181]	MSCs	Human	Around 100 nm	Ultra-centrifugation	In vitro In vivo	The IVDD model was established by annulus fibrosus (AF) needle puncture	• MSCs-derived exosomes play an anti-pyroptosis role by suppressing the NLRP3 pathway • MSC-derives exosomes treatment inhibit LPS-induced pyroptosis in NPCs • miR-410 derived from MSC exosomes inhibit LPS-induced pyroptosis in NPCs	• MSCs-exosomes and miR-410 treatment alleviated the severity degree of IVDD	LPS (5 mmol L^{-1}) treatment

TABLE 36 (Continued)

Study	Cell type	Species of cell source	Size of EV	Isolation	Model	Modeling method	In vitro appraisement	In vivo appraisement	Additional manipulation
Hingert et al.[1182]	BMMSCs	Human	Average 144 ± 2.22 nm	Serial centrifugation	In vitro	/	• MSC exosomes treatment increased cell viability and proliferation of degenerated disc cells • MSC exosomes treatment induced early production of crucial ECM components such as proteoglycan, aggrecan, and collagen type II • EV treatment suppressed apoptosis and the secretion of MMP-1 in disc cells	/	No
Sun et al.[1183]	iMSCs	Rat	80–200 nm	Ultra-centrifugation	In vitro In vivo	The IVDD model was established by annulus fibrosus (AF) needle puncture	• miR-140-5p riched in iMSC exosomes played a pivotal role in the iMSC-sEV-mediated therapeutic effect by upregulating of anabolism markers of the ECM (collagen II and aggrecan), and downregulating of catabolism markers of the ECM (MMP-3 and ADAMTS-4) • iMSC-sEVs could rejuvenate senescent NPCs and restore the age-related function by activating the Sirt6 pathway in vitro	• NPC senescence and IVDD were significantly improved after intradiscally injecting iMSC exosomes	No
Lu et al.[1184]	BMMSC	Human	30–100 nm	Ultra-centrifugation	In vitro	–	• EV treatment increased proliferation activity of NPC • EV treatment generate a healthier extracellular matrix by upregulating expression levels of anabolic/matrix protective genes (aggrecan, collagen II, sox-9 and TIMP-1) and downregulating matrix degrading genes (MMP1 and MMP3)	–	No
Xia et al.[1185]	BMMSCs	Mouse	50–130 nm	Ultra-centrifugation	In vitro In vivo	An IVD degeneration rabbit model was induced with a fine needle puncture	• BMSC-derived exosomes attenuate apoptosis in NP cells treated with H_2O_2 • Exosomes dampen H_2O_2-induced inflammatory marker expression and matrix degradation in NP cells • Exosome attenuate TXNIP–NLRP3 inflammasome activation and caspase-1 cleavage induced by H_2O_2 • Exosomes replenish mitochondrial-related proteins and attenuate mitochondrial dysfunction	• Exosomes attenuate the progression of IVDD • Exosomes delay matrix degradation during the progression of IVDD	H_2O_2 ($500 \times 10\,M^{-6}$)

(Continues)

TABLE 36 (Continued)

Study	Cell type	Species of cell source	Size of EV	Isolation	Model	Modeling method	In vitro appraisement	In vivo appraisement	Additional manipulation
Bari et al.[1186]	ASCs	Human	171.8 ± 18.3 nm	Ultrafiltration	In vitro	–	• At concentrations between 5 and 50 mg/mL, freeze-dried secretome showed to in vitro counteract the oxidative stress damage induced by H_2O_2 on nucleus pulposus cells • Freeze-dried secretome became cytotoxic to NPCs at a concentration of over 50 mg mL^{-1}	–	H_2O_2 ($1 \times 10_M^{-3}$)
Xie et al.[1187]	MSCs	Rat	30–200 nm	Ultra-centrifugation	In vitro In vivo	The IVDD SD rat model was established by needle puncture	• Exosomes reduced apoptosis and calcification of EPCs induced by TBHP • The downregulated level of miR-31-5p in exosomes impaired exosomal protective effects on EPC • miR-31-5p negatively regulated ATF6-related ER stress and inhibited apoptosis and calcification in EPCs	• Sub-endplate injection of MSC exosomes can ameliorate IVDD • Downregulation of miR-31-5p from Exosomes inhibited exosomal protective effects on EPC	TBHP (20×10^{-6} to 60×10^{-6} m)
Liao et al.[1163]	BMMSCs	Human	Average 94.3 nm	ExoQuick reagent	In vitro In vivo	Injection of AGEs into in SD rat tail to induce IVD degeneration	• MSC-exos reduced AGEs-induced ER stress and ameliorated NP cells apoptosis • MSC-exos inhibited the activation of UPR under AGEs-induced ER stress, and decreased CHOP expression • MSC-exos attenuate ER stress-induced apoptosis by activating AKT and ERK signaling in human NPCs	• MSC-exos modulated ER stress-related apoptosis and retarded IDD progression in a rat tail model	AGEs (200 μg mL^{-1})

Note: Reprinted with permission from Lu et al.[1172]

Abbreviations: AFC, annulus fibrosus cell; AGEs, Advanced glycation end products; ASC. adipose-derived mesenchymal stromal cell; BMSC, bone marrow-derived mesenchymal stem cell; CEPC, cartilage endplate chondrocyte; CHOP, C/E homologous protein; EPCs, endplate chondrocytes; ER, endoplasmic reticulum; MSC, mesenchymal stem cell; NPC, nucleus pulposus cell; PLMSC, placental mesenchymal stem cell; TBHP, tert-butyl hydroperoxide; UC-MSC, umbilical cord-derived mesenchymal stem cell; UPR, unfolded protein response.

medicine has been identified for COVID-19, with the exception of three drugs: camostat mesylate, favipiravir, and remdesivir, which acts as an agent against the Ebola virus.[1201] It has been shown that SARS-CoV-2 infection-induced a cytokine storm that may cause ARDS and eventually multiple crucial organ failures. About 80% of COVID-19-affected individuals have minor symptoms that are restricted to the upper respiratory tract, yet in 20% of cases, serious illness results.[1202] There have been dozens of clinical studies focused on the use of exosome therapy for the treatment of COVID-19 in the past 3 years alone, as well as a growing number for the management and mitigation of "long-COVID."[1203–1222]

Despite the fact that there are currently a number of vaccines available to immunize people, scientists worldwide are constantly researching potential treatment approaches to treat infected populations due to the daily discovery of new information regarding the structure, pathogenicity, transmission mechanism, and immunological characteristics of the SARS-CoV-2 virus.[1203–1222]

7.1 | Treatment of COVID-19 using exosomes

As mentioned previously, there is no specific/effective vaccine/therapeutic option for combating the negative effects/side effects of COVID-19 such as the cytokine storm. Previous studies have showed the potential of exosomes for treating SARS coronavirus infection.[1203–1222] In a study by Kuate et al.,[1223] it was demonstrated that exosomes carrying SARS coronavirus spike S protein was successful in inducing neutralizing antibody titers. These results indicated that exosomes can be utilized for treating SARS coronavirus infection.[1223]

A hot topic in the COVID-19 research world is using MSCs in treating the disease. Particularly, exosomes derived from these cells have attracted even more attention because they are much safer. Various studies have investigated the efficiency and safety of using exosomes derived from MSCs in treating patients with COVID-19. For example, Vikram et al. tested the therapeutic potential of bone marrow MSC-Exos in 24 patients infected with SARS-CoV-2 and moderate to severe ARDS.[1224] Introduction of exosomes to patients was shown to be safe and led to significant improvement in the clinical status and oxygenation. A recent clinical trial has investigated the efficacy of inhalation MSC-Exos in alleviating the post-infection symptoms of COVID-19 (NCT04276987).

It has further been shown that MSC-Exos have the ability to promote the survival of alveolar macrophages and change their phenotype from pro-inflammatory (M1) into the anti-inflammatory (M2) polarization.[1225,1226] The implication of these findings is that exosomes can be a viable alternative to their parental cells. Different studies have found that MSC-Exos in the inflammatory environment of ARDS were responsible for reprogramming macrophages from M1-M2 polarization and also improving their phagocytosis effects and oxidative phosphorylation.[1227–1229]

In totality, various studies have generally concluded the following four main advantages with using exosomes for the management and treatment of patients with COVID-19:

1. Protection and proliferation of lung epithelial cells

Preclinical research conducted by many groups has shown that exosomes have a protective function. In one research article, it was shown that lung epithelial cells were protected from oxidative stress-induced cell death by miR-21-5p administration via MSC-Exos.[1230] It was also shown by a different research group that the surface of MSC-Exos expressed Alpha-1-antitrypsin (AAT). Due to its strong inhibitory properties against neutrophil-derived proteolytic enzymes, the anti-inflammatory and immunomodulatory properties of AAT plays a vital role in preserving lung epithelial cells.[1231]

2. Reversal of lung inflammation

The pro-inflammatory response may be a key factor in the pathophysiology of CoVs, according to data from very ill patients. Release of pro-inflammatory cytokines and chemokines is seen in macrophages, dendritic cells, and respiratory epithelial cells during the early stages of CoV infection.[1232,1233] However, throughout the subsequent phases, these cells exhibit diminished secretion of antiviral factors, namely interferons (IFNs), while displaying elevated levels of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and IL-6, as well as chemokines including CCL-2, CCL-3, and CCL5. The delayed but heightened presence of pro-inflammatory substances leads to the occurrence of a "cytokine storm," which has the potential to cause organ damage. Consequently, this phenomenon represents a significant issue that contributes to the severity of the illness.[1234] Immunosuppressive drugs are given to these individuals, which is unavoidably linked to a higher risk of infection.[1235] Due to their established ability to modulate the immune system, MSCs and their exosomes that are derived from them have been studied in a number of preclinical and clinical contexts.

An interestingly comparable state is seen in lung illness linked with graft-versus-host disease (GvHD).[1236,1237] MSC-Exos have been proven in an early clinical trial to reduce grade IV GvHD patients' symptoms.[740] Despite the fact that there is little information on exosomes' powerful immunomodulatory function in a therapeutic setting. This first investigation strengthens the possibility that exosomes might help treat lung damage caused by "cytokine storms."

3. Polarization of lung macrophages

As previously reported, a cytokine storm is produced during a viral infection as a result of an inadequate immune response, which exacerbates lung damage. The lungs' pro-inflammatory macrophages play a major role in mediating this.[1238] Exosome-derived therapy may be a novel way to treat nCOV-associated pathogenicity, according to some preclinical research assessing the impact of MSC-Exos on lung macrophages in diverse lung injury models. These investigations have shown that exosome-derived proteins and a number of miRNAs, including miR-145, facilitate

the regeneration and repair of lung tissue.[130] MSC-Exos may potentially influence the phenotype and function of DCs that infiltrate the lung by promoting the production of immunosuppressive cytokines such as TGF-β and IL-10, which shields the lungs from the systemic immune response that is initiated by DCs and detrimental to macrophages.[1239]

4. Reduction in pulmonary edema and lung protein permeability

Increased protein permeability and alveolar inundation, which culminate in pulmonary edema, are results of infection-induced perturbation of the lung endothelial and epithelial barrier.[1240] Consequently, this impairs the ability of the lungs to exchange air. In a recent study, the authors evaluated the impact of systemically delivered MSC-Exos in a mouse model of acute lung damage caused by *Escherichia coli* endotoxins.[775] These exosomes were shown to lower lung water extravascularly by 43% while also lowering lung protein permeability and pulmonary edema.[775] Later, using human donor lungs that were unsuitable for transplantation, the team showed that these exosomes could restore alveolar fluid clearance (AFC) in an ex vivo lung perfusion model. The capacity of MSC-Exos to internalize into injured host cells was somewhat facilitated by their CD-44-dependent mechanism.[1241]

Therefore, the injection of MSC-Exos has a great potential to repair the patient's damaged lungs via a variety of pathways, and as such, it may be a viable therapeutic nanomedicine intervention for patients in critical condition (Figure 37).

8 | CANCER THERAPY

There is no question that the use of exosomes in the field of cancer has overwhelmingly been utilized as early detection biomarkers.[1243] Since exosomes are more stable than proteins and hormones in the blood, many research groups have favored using exosomes as early biomarkers for cancer detection and disease progression.[1243] Interestingly, since exosomes can also carry signaling molecules, they have more recently been utilized as therapeutic options. The use of exosomes as therapeutic regenerative agents is the main topic of this section. Exosomes may also be effectively used as drug delivery vehicles to treat a variety of malignancies.

8.1 | Breast cancer

In a paper titled: "Exosomes as Emerging Drug Delivery and Diagnostic Modality for Breast Cancer: Recent Advances in Isolation and Application," Kumar and colleagues shed light on the potential use of exosomes for the diagnosis and treatment of breast cancer.[1244] Lung cancer is the most common cancer worldwide, with breast cancer coming in second.[1244]

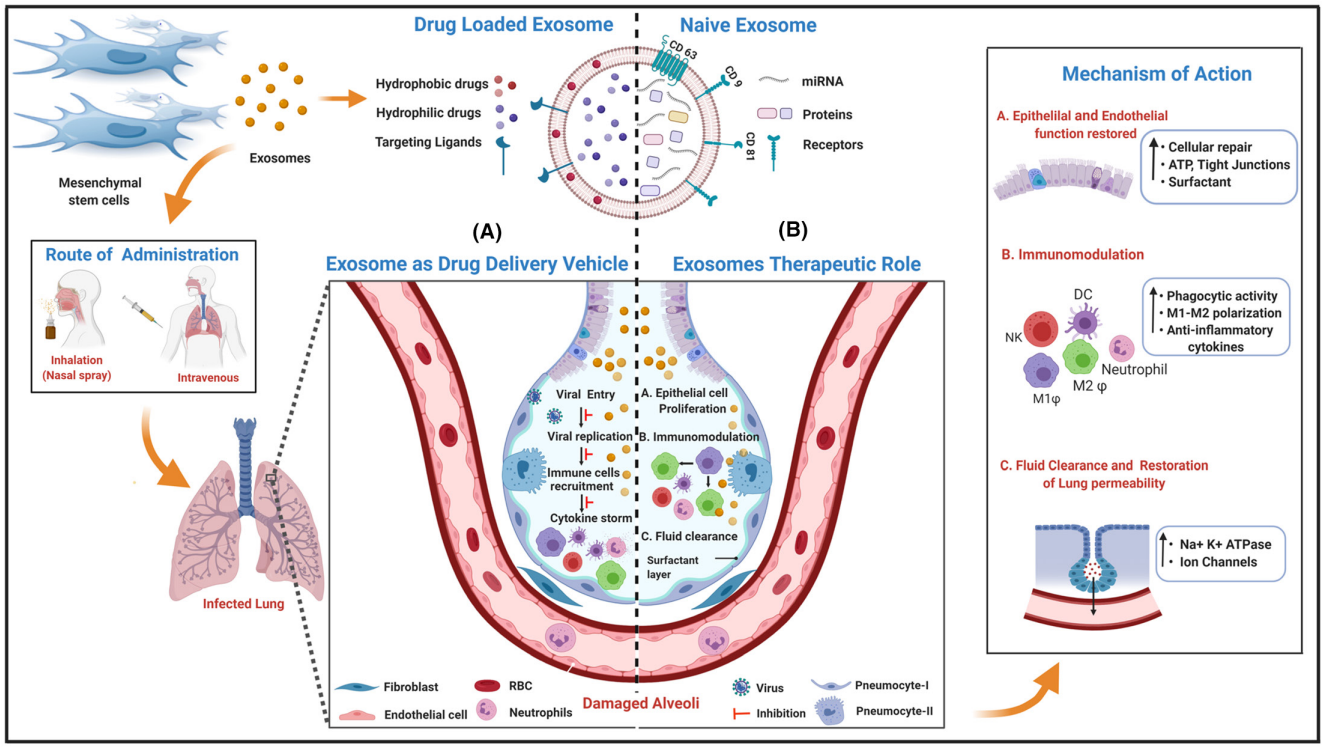

FIGURE 37 Schematic representation showing the potential role of MSCs-derived exosomes in combating COVID-19 Infection. Panel (A) synergistic effect of the drug and exosomes may be utilized as an effective approach against the virus. Various hydrophobic and hydrophilic drugs with antiviral properties can be packaged into exosomes for its delivery to the target site. Panel (B) The therapeutic cargo present in Exosomes aids in the reduction in inflammation, cellular repair, alveolar fluid clearance, and other damage caused to the lung during viral infection. Reprinted with permission Pinky et al.[1242]

Chemotherapy, immunotherapy, radiation, and surgery are all used to treat breast cancer. Chemotherapy has been the mainstay of cancer treatment among these medicines; nonetheless, it comes with a number of adverse effects, including nephrotoxicity, hair loss, vomiting, and neurotoxicity. Novel medication delivery techniques that avoid the mentioned negative effects and deliver the right pharmaceuticals to the intended spot have emerged as a result of these disadvantages. Exosomes are thought to be a newly developed, innovative drug delivery mechanism that offers a flexible platform for both medication administration and diagnostics.

Exosomes are being used in clinical studies to treat breast cancer. These trials are based on several reports that show enormous scientific effort that produced favorable results.[1244] The present human exosome experiments are mostly focused on discovering possible exosomal biomarkers in various bodily fluids (particularly blood and urine) for early cancer diagnosis, even if the notion remains far from practical reality. Proteomic analysis of 72 breast cancer patients' exosomes obtained from the cerebral fluid is part of an ongoing clinical investigation on exosomes used to diagnose leptomeningeal metastatic breast cancer.[1244] In a related clinical investigation; exosomes were extracted from breast cancer patient's blood and urine samples in order to measure the stress protein (HSP 70), which is thought to be a tumor biomarker.[1244] Exosomes are being considered for use in chemotherapy in addition to their use as biomarkers.[1244] To measure the expressed HER2 and HER3 dimers over the isolated exosomes, for example, has allowed scientists to identify HER2 type breast cancer. This is because the HER2 receptors are also discovered to be overexpressed on the surface of exosomes. Exosome loading may also be used to determine the impact of pembrolizumab on the tumor microenvironment in a similar manner.[1244]

While this field is still in its infancy, there is tremendous upside currently for the use of exosomes in breast cancer therapy. Future years of research should lead to novel discoveries and will likely garnish mainstream momentum in the coming decade.

8.2 | Colorectal cancer

Globally, colorectal cancer (CRC) is the second most common cause of cancer-related deaths. It is a cancer that emerging from the colon or rectum.[1245] Of all CRCs, 72% are caused by colon cancer and 28% by rectal cancer.[1246] An adenocarcinoma originating from the colon's and/or rectum's glandular epithelial cells accounts for about 90% of colorectal cancer cases. The greater death rate associated with CRC is mostly caused by its advanced stage of diagnosis. 64% of CRC patients survive for 5 years, compared to only 12% of those with metastases.[1247]

In a study titled: "The therapeutic potential of stem cell-derived exosomes in the ulcerative colitis and colorectal cancer," Guo et al.[1248] discovered that exosomes produced from different MSC sources, such as olfactory ecto-MSCs (OE-MSCs), human umbilical cord-derived MSCs (hUC-MSCs), human ADSCs, and human BMSCs, demonstrated a protective function against ulcerative colitis (UC) and colorectal cancer (CRC). It has been discovered that exosomes from OE-MSCs, ADSCs, hBMSCs, and hUC-MSCs, can improve experimental UC by suppressing inflammatory cells such as macrophages and Th1/Th17 cells, lowering the expression of pro-inflammatory cytokines, and stimulating Treg and Th2 cells' anti-inflammatory function and increasing the expression of anti-inflammatory cytokines. Furthermore, it has been shown that tumor-suppressive miRs (miR-3940-5p/miR-22-3p/miR-16-5p) included in hUC-MSC-Exo and hBMSC-Exo inhibit the growth, migration, and invasion of colorectal cancer cells via controlling the RAP2B/PI3K/AKT signaling pathway and ITGA2/ITGA6.[1248]

Consequently, and to summarize, MSC-Exos have positive effects on UC and CRC by means of two distinct processes, namely immune response modulation and antitumor response induction, respectively. Table 37 highlights these interactions and the advantages of exosomes over their parent MSCs.

TABLE 37 Major differences between MSC and MSC-derived exosome in colorectal cancer.

	MSC	MSC-derived exosome
Therapeutic effects	Cancer immunotherapy, regeneration medicine, and immunomodulation	Cancer immunotherapy, regeneration medicine, and immunomodulation
Drug and nucleic acid delivery	Only limited drugs could be internalized by MSC, such as paclitaxel and gemcitabine, transfection efficiency is a major limitation for nucleic acid delivery	Promising carriers for all type of drugs, also for nucleic acid with increased efficiency compared to MSC
Target tissue	Injured site	Injured site
Immunogenicity	Can be allogenic for the immune system	Non-immunogenic
Clinical application in CRC	Preclinical and clinical application	Currently in preclinical applications
Production	Undergo senescence after only a few passages, expensive to have large-scale production	No senescence and easy to generate a large-scale production for clinic application

Note: Reprinted with permission from Guo and colleagues.[1248]

8.3 | Gastric cancer

The prognosis for gastric cancer (GC), a frequent malignant tumor that affects human health, is poor, and it often has an obscure origin. It is the fourth most frequent cancer overall and the third leading cause of cancer-related deaths globally. Approximately 1.089 million new cases and 768000 deaths of GC occur each year.[1249] Interestingly, various research groups have found that exosomes play an important role in the invasion and metastasis of gastric cancer and can be, therefore, used as very early detection tool for diagnosis.[1250] Age-standardized five-year survival rates for GC are estimated to be between 20 and 40 percent because of delayed diagnosis, a dismal prognosis, and ineffective treatment.[1251,1252] In a paper titled: "Exosomes and Exosomal circRNAs: The Rising Stars in the Progression, Diagnosis and Prognosis of Gastric Cancer,"[1250] Lu and colleagues discussed the potential of exosomes as new biomarkers in the field and thoroughly point to their potential as future applications as mainly diagnosis markers but with the ability to be utilized as therapeutic options once their implication and cargo are fully understood.

8.4 | Osteosarcoma

The most frequent bone tumor that affects children and teenagers is osteosarcomas. In a study titled: "Exosomes as Efficient Nanocarriers in Osteosarcoma: Biological Functions and Potential Clinical Applications," Yang et al.[1253] overviewed the state of exosome research in the field of osteosarcomas, emphasizing both the biological roles of osteosarcoma exosomes and their use as therapeutic targets and diagnostic indicators in the disease.

Exosomes have significant roles in osteosarcomas, indicating that they may be explored as therapeutic targets as well. The osteosarcoma derived exosomal biomarkers mentioned above could also be utilized as therapeutic targets of osteosarcomas. According to Baglio et al., functional TGF-b molecules are present in the exosomes secreted by osteosarcomas, and these molecules enhance IL-6 expression, thereby promoting osteosarcoma growth and metastasis formation. Combining TGF-b inhibitors with IL-6 blocking agents has been shown to halt osteosarcoma progression while lowering drug resistance.[1254] Notaro et al. have recently shown that the synthetic agonist of cannabinoid receptors, WIN, significantly increased the number of exosomes released. Additionally, isolated exosomes from WIN-treated cells had strong anti-migratory effects on osteosarcoma cells that were not receiving treatment, suggesting that WIN-treated cells may provide a novel therapeutic agent for osteosarcoma therapy.[1255]

Additionally, exosome-derived RNAs may be used as osteosarcoma therapeutic targets, according to recent research. Zhang et al.[1256] showed that miR-206 generated from BMSC exosomes might enter osteosarcoma cells and halt the growth of the tumor by focusing on TRA2B. Exosome-derived miR-101 has been shown in research by Zhang et al.[1257] to have metastasis-inhibitory characteristics in osteosarcomas. Ye et al.[1258] found that patients with osteosarcomas have many dysregulated exosome-derived miRNAs. Wang et al.[1259] demonstrated that the exosome-derived miR-1228 might promote osteosarcoma invasion and migration by downregulating the mRNA expression of SCAI in osteosarcomas. These studies, among others, highlight the potential for novel therapeutic targets for osteosarcomas with the use of exosomes. Furthermore, an additional review article focuses on the unique structure and relevant characteristics of exosomes as promising nanocarriers for osteosarcoma treatment.[1260]

9 | OTHER THERAPEUTIC USES OF EXOSOMES

Lastly, there have been a number of other uses of exosomes for various illnesses that fall into random categories. Within this section, the therapeutic use of exosomes will be briefly mentioned regarding its use for the management of infertility, obesity, and sleep apnea.

9.1 | Infertility

In a study titled: "Mesenchymal Stem-Cell Derived Exosome Therapy as a Potential Future Approach for Treatment of Male Infertility Caused by Chlamydia Infection," Izadi et al.[1261] studied the use of exosomes on male infertility following infection. Unfortunately, male fertility, sperm function, and the reproductive tract are all negatively impacted by microbiological sexually transmitted infections (STIs). Since STIs often have no symptoms and may lead to serious side effects, including fibrosis, scarring, and urogenital inflammation, optimal treatments should be performed to prevent the noxious effect of STIs on male fertility.[1261] Chlamydia trachomatis stands out as the prevailing bacterial sexually transmitted infection (STI) that often presents without symptoms, and that may have an effect on male fertility and sperm quality. The therapeutic potential of exosomes derived from MSCs has attracted increasing attention in recent years. These exosomes are of interest because they may modulate immunity, reduce inflammation, neutralize free radicals, and promote tissue repair. Importantly, they provide these benefits without the potential drawbacks associated with traditional stem cell transplantation-based treatments. Exosome therapy, being a noninvasive modality, has shown encouraging outcomes in terms of its potential to facilitate the regeneration of impaired sperm and the treatment of asthenozoospermia.[1261]

Exosomes have shown promise in restoring spermatogenesis and sperm regeneration in animal studies. One study found that exosomes derived from amniotic fluid could restore sperm parameters like motility and concentration, as well as the number of spermatocytes and spermatogonia, and ultimately male fertility.[1262] Exosomes have also been shown to increase post-thaw sperm parameters and have a protective impact against oxidative stress caused by the cryopreservation procedure and sperm cryoinjuries

(such as cell membrane damage and DNA damage).[1263,1264] It is interesting to note that treating spermatozoa with MSC-Exos might enhance sperm sticky and fusogenic qualities by shuttling adhesion molecules, including CD44, CD29, CD54, and CD106, in addition to increase sperm characteristics after frozen–thawed sperm.[1265] Furthermore, a number of clinical experiments (NCT01159288, NCT03608631, and NCT01294072) have shown that exosomes may be loaded with medications or bioactive molecules for therapeutic purposes (NCT04276987, NCT03437759, NCT04213248, and NCT04602442).[1266]

In conclusion, exosomes have been shown to have a significant impact in mitigating the effects of infection, including inflammation, cell damage, fibrogenesis inhibition, and scar formation.

9.2 | Obesity

Obesity is distinguished by the presence of low-grade, persistent inflammation, which contributes to the development of insulin resistance and diabetes.[1267] The presence of obesity has been associated with the onset and advancement of certain autoimmune disorders, such as thyroid autoimmunity, inflammatory bowel disease, psoriasis, psoriatic arthritis, and rheumatoid arthritis. The aforementioned issue poses a significant risk to public health, exceeding the magnitude of both the ongoing opioid crisis and the prevalence of cancer. In addition to the deposition of excess adipose tissue and a reduction in the body's resting metabolic rate, obesity is also associated with an elevated prevalence of type-2 diabetes mellitus, hypertension, atherosclerosis, hyperlipidemia, and cardiovascular disease.[1268,1269]

By decreasing regulatory T cells (Tregs), raising Th17 and Th1 immune responses, and producing inflammatory cytokines, these illnesses are caused by a change in self-tolerance that promotes a pro-inflammatory immune response.[1267] Therefore, in order to create treatments that lower the risk of autoimmune disorders and other immunological issues, it becomes imperative to understand the immunological alterations that result in this low-grade inflammatory milieu. Patients that are obese and have a high BMI release a large amount of microvesicles and exosomes from their adipocytes and immune cells.[1267] While presently much research is focused on understanding these secreted exosomes during pathogenesis,[1267] eventually, exosomes could be engineered to lower inflammation and potentially reverse some of the compounding negative effects of obesity on overall health.

9.3 | Sleep apnea

In the review article titled: "The Mystery of Red Blood Cells Extracellular Vesicles in Sleep Apnea with Metabolic Dysfunction," the role of red blood cell exosomes was revealed as a contributing factor to sleep apnea and overall body inflammation.[1270] Humans sleep for around one-third of their lives, making it an essential component of living. It is obvious that inadequate sleep, particularly in the form of psychiatric problems like depression or stress, may lead to poor mental performance, daytime lethargy, and decreased attentiveness.[1271] Both genders are affected by sleep-disordered breathing (SDB), which is often linked to a broad range of co-morbid illnesses in many organ systems.[1272]

OSA has become a significant public health issue, and mounting data indicates that untreated OSA may contribute to the onset of a number of illnesses, including neurological disorders as well as failing organs.[1267,1270] Moreover, OSA may cause blood oxygenation to drop and the sleep cycle to become fragmented. Free radicals, or ROS, have the capacity to generate and combine with NO to create peroxynitrite, which reduces NO's bioavailability. The characteristic of OSA, hypoxia, is a decrease in tissue oxygen saturation that impacts several cell types, with cell-to-cell communication being essential to the result of this interaction. Although mostly known for their function as oxygen and nutrition carriers to tissues, red blood cells (RBCs) also play important roles in viscosity, blood rheology, redox regulation, and systemic NO metabolism control. It has been shown that RBCs enhance cardiac damage and cause endothelial dysfunction.[1270] Exosomes, which are released by RBCs in both healthy and pathological circumstances, may be essential for the identification of hypoxic situations and for facilitating their restoration. The molecular connections between alterations in RBC functional characteristics and cardiovascular disease are extensive. Thus, increasing our understanding of the pathophysiological significance of RBC-EVs and their methods of generation may aid in clarifying the nature of circulating EVs and facilitating their use in therapeutic settings.

10 | DISCUSSION AND CONCLUSIONS

The present scoping review highlights the many applications of exosomes across many fields of medicine. Exosomes are among key paracrine effectors secreted by MSCs and due to their biological cargo, which is similar to parental cells, and their ability to preserve healing properties, they are considered as an attractive candidate to replace MSCs in treating various diseases and affecting many organs (Figure 38).[1273] Nontoxicity, low immunogenicity, high stability, easy storage, and the potential to be produced as an off-the-shelf product are several benefits of exosomes compared to their cellular counterparts that led to their expanding clinical application as new therapeutic surrogates.[1274]

Recent research conducted by Hosseini et al., the authors emphasized five significant benefits of exosomes compared to their parent cells. These included[1205]:

- The analysis of exosomes' activity and their originating cell demonstrates that exosomes may have the same effect by either a distinct or comparable mechanism, and in several instances, they are far more potent.[1275] Del Fattore et al. demonstrated that MSC-Exos had superior immunomodulatory capabilities compared with the parent cells. It was shown that MSC-Exos, which

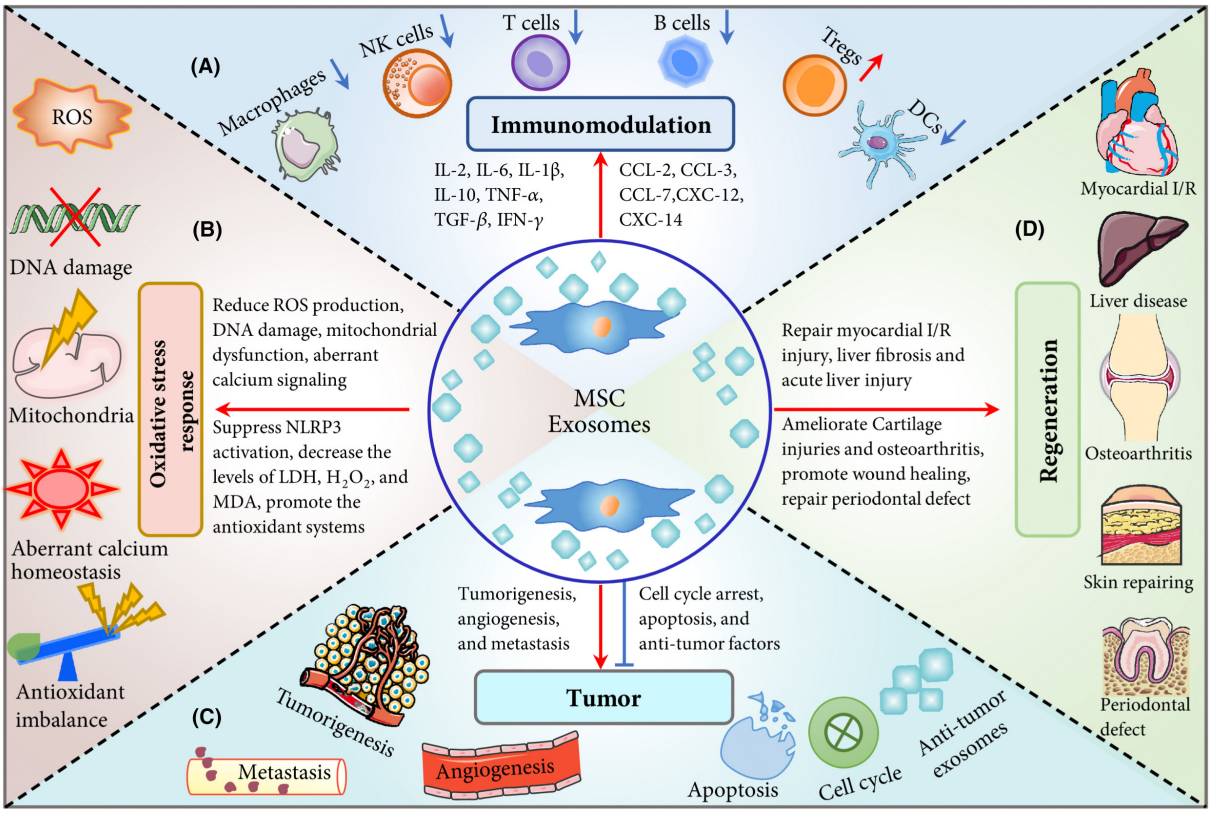

FIGURE 38 Biological mechanisms of MSC exosomes. (A) Immunomodulatory effects of MSC exosomes. (B) Reactions of MSC exosomes in response to oxidative stress. (C) Interactions between tumor cells and MSC exosomes. (D) Applications of MSC exosomes in regenerative medicine. CCL, C-C motif ligand; CXC, C-X-C motif chemokine; DCs, dendritic cells; I/R, ischemia/reperfusion; IFN-γ, interferon γ; IL, interleukin; NK cells, natural killer cells; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; Tregs, regulatory T cells. Reprinted with permission from Shen and Chen.[747]

likely have different characteristics than parent cells, modify the ratio of Treg/Teff cells in P-MSCs and raise the levels of anti-inflammatory cytokines, such as IL-10.[1276]

- Exosomes, because of their diminutive size, may easily traverse narrow blood vessels and even the blood–brain barrier. In contrast, MSCs are prone to being lodged in the lungs and causing pulmonary embolism and infarction, particularly after intravenous administration.[1277] Because of their enormous size (and 25 mL in suspension), inosine-labeled MSCs showed a significant initial uptake when injected intravenously and trapped a substantial number of cells in the lungs.[1278]
- Exosomes generated from MSCs, whether autologous or allogeneic, pose no threat since they do not include MHC class I or II on their surface. A recent prospective non-randomized cohort trial was conducted to assess the safety and therapeutic effectiveness of exosomes produced from allogeneic BMSCs in COVID-19 patients.[1224] All safety objectives were satisfied after 72 h of a single intravenous injection of exosomes, and no adverse effects were noted. While 24 individuals were observed, 17 (or 71% of the total) made a full recovery. The ability to restore patients' oxygenation further improved under these simple clinical settings. An increase in lymphocyte and neutrophil counts, as well as a decrease in acute phase reactants, C-reactive protein, and ferritin, were all indicators of immune reconstitution in the laboratory results. Along with that discovery, scientists also announced that exosomes produced from MSCs are a promising new treatment option for severe COVID-19.[1224] As mentioned before, there is still cause for worry about MSCs' aberrant differentiation and spontaneous transformation.
- Exosomes are harvested much simpler and much more affordable to produce and freeze-store grade-clinical exosomes in accordance with GMP standards.[1279] As an example, quality control for exosome manufacture might begin with the donor competence analysis and be used throughout the whole process. Another example of a closed-loop system would be the possibility of completely automating some manufacturing operations, such as final concentration and vial filling. Every batch of exosomes is tested for size, homogeneity, number, and positive and negative indicators in the final product.[1280]
- Effortless manipulation of exosomes and the ability to design them enables the creation of a diverse array of products customized for specific purposes using a variety of direct and indirect methods. Enhancing the therapeutic efficacy of exosomes may be achieved by including medicinal medicines within the exosomes

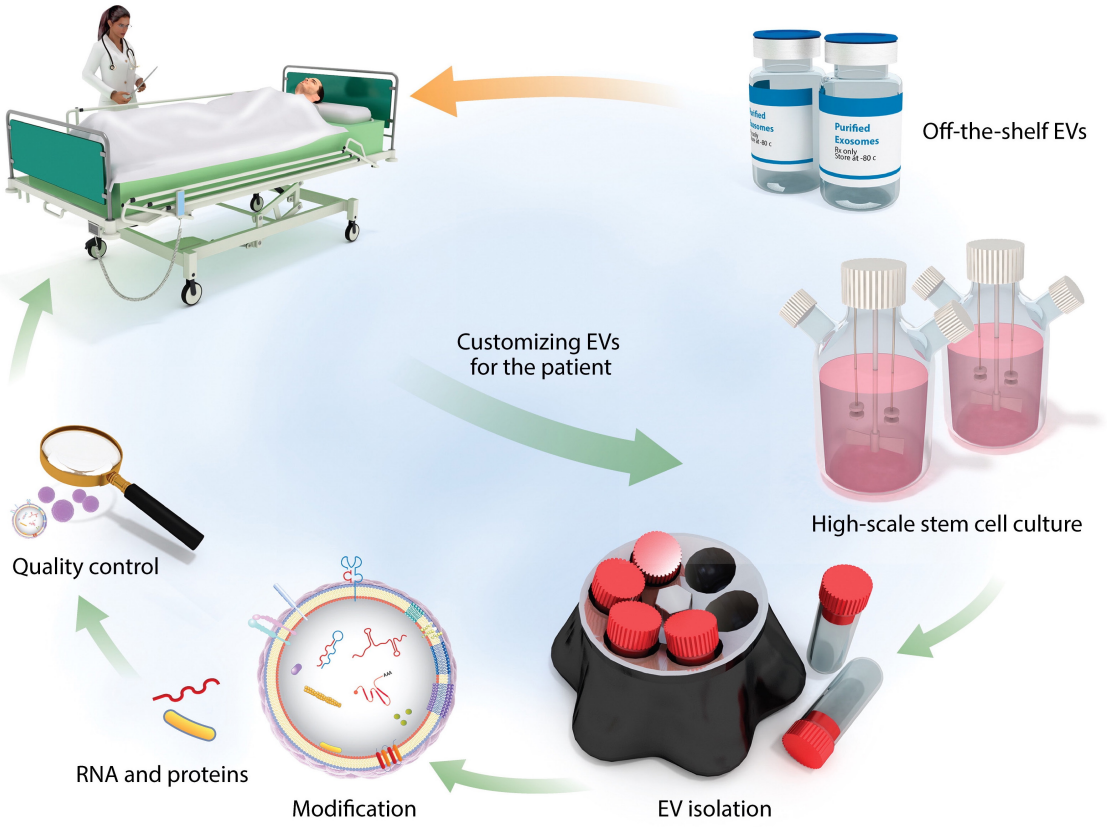

FIGURE 39 Stem cell extracellular vesicles (EVs) for clinical applications. EVs are designed, manufactured, and quality controlled beforehand and stored as off-the-shelf medications to be infused in patients as needed. Other EVs may also be customized accordingly for the individual patient by harvesting autologous stem cells, expanding, and modifying them, producing EVs, and infusing them back to the same patient. In this process, the stem cells can also be genetically modified, and their EVs may undergo further modification by loading them with therapeutic molecules. Finally, EVs need to undergo quality control and be stored for future administration. Reprinted with permission from Riazifar et al.[1282]

are deriving them from various sources depending on the clinical indications.[129,1281]

To date, over 600 clinical trials (registered, ongoing, and completed) worldwide using EVs in diagnostic and therapeutic capacities will pave way to their future use in standard clinical practice. Many open questions remain including the exact signaling molecules required in various exosomes for the treatment of various illnesses. For instance, exosome content may be vastly different in signaling molecules to treat Parkinson's disease versus osteoarthritis of the knee. While these open questions remain, positive outcomes from various MSC-sourced exosomes have shown benefit across practically all fields of medicine. Figure 39 depicts the future clinical challenges toward commercializing and utilizing exosomes in every day clinical practice. The number of studies (over 5000 publications yearly) and human clinical trials will certainly pave way toward a tremendous future of clinical practice using exosomes.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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